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Stereopsis and Unequal Luminosities of the Images in the Two Eyes
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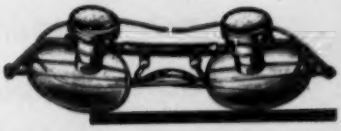

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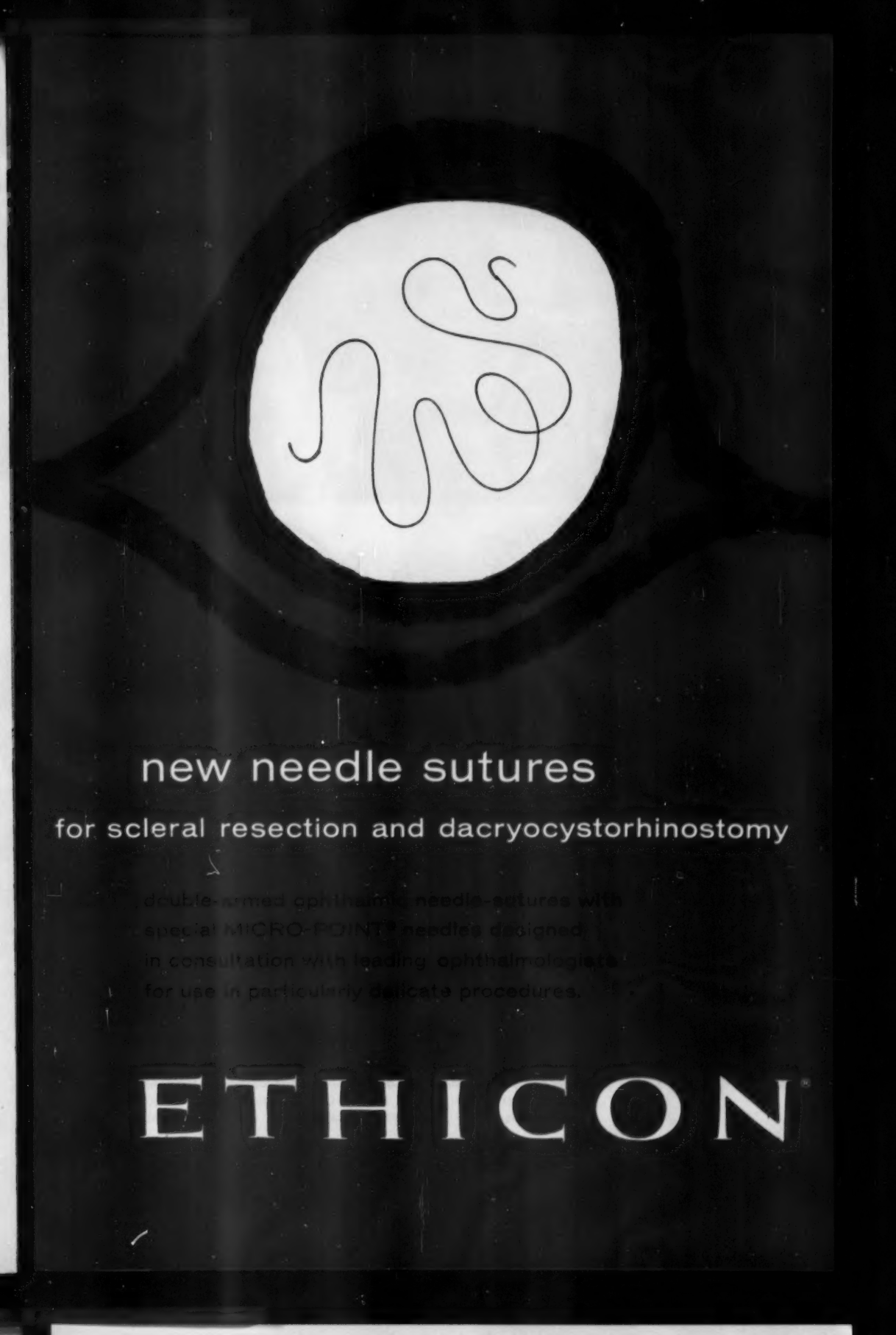
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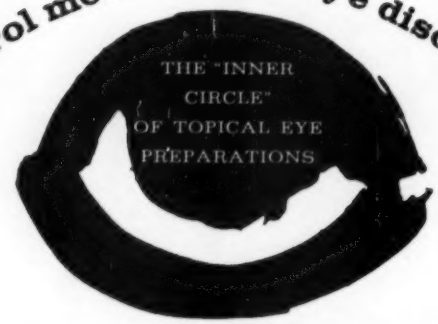

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Use and Misuse of Acetazoleamide (Diamox) in the Treatment of Glaucoma

PAUL A. CHANDLER, M.D., Boston

Since the discovery [1,2] that the carbonic-anhydrase-inhibiting drug acetazoleamide (Diamox) brings about a lowering of the intraocular pressure, its use has been widespread in the treatment of glaucoma. Its pressure-lowering effect is due solely to a lessening of the rate of aqueous production. The obstruction to outflow of aqueous is uninfluenced by acetazoleamide. Thus the use of this drug in the treatment of glaucoma must be regarded as a palliative treatment, since it in no way affects the fundamental cause of increased intraocular pressure—obstruction to outflow. Such palliative treatment is often of tremendous value in preventing damage to vision while other measures are employed to relieve the fundamental difficulty—obstruction to outflow of aqueous. This principle is employed in other ophthalmological problems. Thus the use of steroids in certain inflammatory ocular conditions, while not affecting the fundamental disease process, may lessen the inflammatory manifestations and protect the eye from irreparable damage while other measures are employed to combat the disease itself. It has been said that steroid therapy never cures a disease but may lessen its severity and prevent undesirable consequences of the disease. Similarly, acetazoleamide never cures glaucoma, but it may lessen its severity while the drug is employed.

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Any new and valuable addition to our therapeutic armamentarium is usually hailed with enthusiasm and may be used unwisely. This has been true of the sulfonamides and antibiotics and of the steroids. It is becoming increasingly apparent that acetazoleamide is being unwisely used in the treatment of some forms of glaucoma. Its greatest field of usefulness is in the treatment of secondary glaucoma. Secondary glaucoma, by definition, is a rise in ocular tension secondary to some other eye disease. If the fundamental disease can be cured, the secondary glaucoma is likewise cured. Where formerly palliative surgical procedures were frequently employed in cases of secondary glaucoma to prevent serious damage to the vision from increased tension while the disease was running its course, now acetazoleamide serves the same purpose and has proven to be of tremendous value.

In open angle glaucoma at all stages of the disease the angle is always open, and thus aqueous always has access to the filtration apparatus. The obstruction to outflow which results in increased ocular tension resides somewhere in the filtration apparatus. This form of glaucoma is treated by miotics and, when it is uncontrolled, by various filtering operations to increase drainage from the anterior chamber. In this form of glaucoma, acetazoleamide, if tolerated by the patient, may be used at any stage of the disease. Its pressure-lowering effect as an adjunct to miotic therapy may protect the

eye from damage while it is being used, so that in some cases operation can thereby be avoided. The use of acetazoleamide has no deleterious effect on the disease itself. It does not lessen the effectiveness of any other form of therapy, either medical or surgical, and thus in open angle glaucoma there is no contraindication to its use save the unpleasant side-effects experienced by some patients.

In angle closure glaucoma, the situation is quite different. Here the obstruction to outflow is due solely to closure of the angle. The outflow channels, at least in the early stages of the disease, are completely normal, and tension rises and falls as the angle closes and opens either spontaneously or under the influence of miotics. The level of tension is a fairly accurate guide as to the extent of the angle which is closed at a given time. Thus in a case of angle closure glaucoma at a time when the tension is normal, either spontaneously or under the influence of miotics, one can assume, and gonioscopy confirms the assumption, that the angle is completely open or nearly so. In another case, if the tension is considerably elevated one can assume that a considerable extent of the angle is closed, and gonioscopy confirms this assumption. It is a well-known fact that in angle closure glaucoma, if the tension remains elevated and the angle closed, sooner or later this portion of the angle becomes permanently closed by peripheral anterior synechias. Though the tendency to the formation of permanent peripheral anterior synechias varies greatly in different eyes, it is an ever-present danger, and it is impossible to predict in a given case whether or not anterior synechias will form after a single episode of closure or only after repeated closures. Treatment of angle closure glaucoma of whatever type is predominantly surgical. Iridectomy results in widening of the chamber angle and in the opening of all portions of the angle not already permanently closed by synechias. In an early case, where there are only a few or no peripheral anterior synechias, peripheral iridectomy effects a complete and permanent cure. If operation is deferred until a considerable portion of the angle is permanently closed by synechias, a filtering operation is required, and in these neglected cases all operations may fail and the eye may be lost. Thus it can be seen that here is a form of glaucoma in which in the early stages a simple surgical procedure effects a complete cure of the disease and in the late stages all treatment may fail. This is well recognized and documented by wide experience.

Now, if acetazoleamide is employed along with miotics in the treatment of angle closure glaucoma the level of tension is no longer a guide as to the extent of closure of the angle. Without acetazoleamide, a rise in tension to 40 or 50 mm. Hg means closure of a considerable portion of the angle, and this would be an indication for early surgical intervention to forestall permanent closure by synechias. If in such a case acetazoleamide is used, tension usually falls to the normal range, thus giving a false sense of security, while the angle may remain closed. If this treatment is continued, sooner or later the angle may be permanently closed by synechias, the chance for relief of the glaucoma by simple peripheral iridectomy has been lost, and there is now a permanent glaucomatous state. Gradually more and more of the angle closes, and, in spite of miotic therapy and acetazoleamide, tension eventually rises and a more formidable operation has to be undertaken. Now only a filtering operation will suffice, and since a large portion of the angle is closed by peripheral anterior synechias only very free filtration will keep the tension at normal levels. Aside from the possibility of failure of the eye to develop a filtering scar and hence failure of control of tension, the operative hazards are far greater with filtering operations than with iridectomy.

Once operation is decided on in angle closure glaucoma and the patient is being prepared for operation, acetazoleamide is a most valuable adjunct to therapy. One sees patients with acute glaucoma in whom miotic therapy alone fails to lower the tension but in whom the tension can be brought

to normal if acetazoleamide is also employed. In subacute angle closure glaucoma acetazoleamide used in the immediate preoperative period is very valuable in reducing the tension and thus lessening the operative risk. Thus, as an immediate preoperative treatment acetazoleamide serves a very useful purpose in all types and stages of angle closure glaucoma. However, in my opinion, it should never be used as a continuing treatment in any form of angle closure glaucoma as a substitute for prompt operation, since it masks the danger signs and symptoms, as does morphine given for abdominal pain, and may lead to disastrous delay in definitive surgical treatment. After operation for angle closure glaucoma, either iridectomy or a filtering procedure, there may be a certain amount of residual glaucoma. Operation has opened all portions of the angle not permanently closed by synechias, and no further closure will take place. The residual glaucoma is now a permanent state and will not become significantly better or worse as time passes. In some cases further operation is required, but in many instances the residual increased tension can be controlled by medical means. Here there is no contraindication to the use of acetazoleamide, and it may be used freely, since there is no longer the problem of further closure of the angle, and no longer the problem of masking the signs and symptoms. It is simply a question of controlling the residual increased tension by all the means available.

Acetazoleamide is a most valuable addition to our medical armamentarium in the management of glaucoma. Its greatest field of usefulness is in the secondary glaucomas, but it is often very helpful in open angle glaucoma. I believe it has no place in the treatment of angle closure glaucoma except in the immediate preoperative period and as a postoperative treatment for residual glaucoma.

5 Bay State Rd.

Report of Cases

CASE 1.—A 51-year-old woman was first seen by me on May 7, 1956. There was a history of an acute attack of glaucoma in the left eye in July, 1955. An ophthalmologist prescribed a miotic at that time, and tension fell to normal levels. The patient continued to use a miotic. From time to time the patient experienced transient blurring of vision in the left eye. Another fairly severe attack of glaucoma occurred in April, 1956, with a tension of 60 mm. Hg. At this time acetazoleamide was prescribed and the miotic was continued. On a regimen of 4% pilocarpine four times a day and 250 mg. of acetazoleamide twice a day tension was said to be in the normal range, but it gradually rose. When examined on May 7, 1956, in the right eye vision with glass was 6/5. Tension was 20 mm. Hg. The media were clear; the fundus, normal. Gonioscopy revealed an excessively narrow angle everywhere open.

In the left eye vision with glass was 6/12. The cornea showed epithelial edema. The media were clear. The disc showed shallow, saucer-like cupping. Tension was 67 mm. Hg. Gonioscopy carried out after clearing the cornea with glycerin revealed an angle completely closed, except at the 2 o'clock position, in the upper nasal quadrant. Tension could not be materially reduced by intensive miotic therapy.

A prophylactic peripheral iridectomy was done on the right eye, and an iridencleisis, on the left.

The postoperative course was uneventful. When the eyes were quiet gonioscopy of the right eye showed the angle everywhere open and strikingly wider than before operation. In the left eye the angle was found to be completely closed by peripheral anterior synechias, except the 2 o'clock position, above and nasally. An obviously functioning cystic filtering scar was evident. In spite of this and the use of 4% pilocarpine tension has ranged from 26 to 35 mm. Hg. It is possible that further operation will be re-

quired, but acetazoleamide will be tried first if there is evidence of loss of field.

Comments.—After the first attack, when tension was readily normalized with miotics, a peripheral iridectomy would undoubtedly have resulted in a complete and permanent cure of the glaucoma. It is probable that the same would have been true after the second proven attack if it had been done promptly. However, acetazoleamide lowered the tension to reasonable levels for a while, until in the end the angle was almost completely closed and tension rose in spite of miotic and acetazoleamide therapy. This eye is, therefore, almost completely dependent on artificial filtration to control the tension. Thus, in spite of an adequate appearing filtering scar the tension is not completely controlled. If acetazoleamide had not been used after the second proven attack, the tension would undoubtedly have been high enough to demand prompt operation, which might then have been done before nearly the entire angle was permanently closed by peripheral anterior synechias. Acetazoleamide therapy gave a false sense of security while the angle became almost completely closed.

Case 2.—In January, 1956, a 61-year-old man began to see colored haloes about lights with the left eye. After a few days an ophthalmologist was consulted, who found considerable elevation of tension in the left eye. A miotic was prescribed, and tension promptly fell to normal. Treatment of both eyes with a miotic was continued. After two or three months haloes were again seen with the left eye and tension was found to be elevated. The miotic was continued, and acetazoleamide was prescribed. Again tension fell to the normal range, but in November, 1956, the patient again saw haloes about lights. When first examined by me, on Nov. 27, 1956, vision in the right eye was 6/6 with glass. The anterior chamber was shallow; media, clear; fundus, normal. Tension was 17 mm. Hg. Gonioscopy revealed an excessively narrow angle, open throughout. Field was full.

In the left eye vision with glass was 6/6. Anterior chamber was shallow; media, clear; fundus, normal, except that the physiologic cup was slightly wider than in the right eye. Tension was 48 mm. Hg. The field was full. Gonioscopy revealed an area of probable open angle between 8:30 and 10 o'clock. The remainder of the angle was closed.

Intensive miotic treatment failed to lower the tension, and an operation was performed on Nov. 28, 1956. A peripheral iridectomy was done with an attempt to free peripheral anterior synechias over the upper half of the angle. Air was injected into the anterior chamber at the end of the operation. The following day, Nov. 29, 1956, a prophylactic peripheral iridectomy was done on the right eye. Three days later tension in the left eye rose to 50 mm. Hg. Gonioscopy revealed the angle in the right eye to be everywhere open and strikingly wider than before operation. In the left eye the angle appeared to be completely closed. The anterior chambers were shallow but of equal depth in the two eyes. Tension in the left eye fell to 20 mm. Hg under treatment with miotics and acetazoleamide.

On Dec. 6 an iridencleisis with sclerectomy was done on the left eye. The anterior chamber remained flat after the operation. Tension was soft on Dec. 7 and on the morning of Dec. 8. In the evening of Dec. 8 tension in the left eye was 55 mm. Hg. Treatment with miotics and acetazoleamide was begun. Tension was normal the following morning. On Dec. 12 tension remained normal and the anterior chamber was formed but very shallow. Acetazoleamide was discontinued. Tension remained normal until Dec. 28, when it was found to be 28 mm. Hg. The following day the anterior chamber was entirely flat and tension was 40 mm. Hg. On Dec. 19, 1956, a posterior sclerotomy with release of a considerable quantity of vitreous and air injection into the anterior chamber was done. After absorption of the air, the anterior chamber remained formed, but it was more shallow than in the right eye. Tension re-

mained low until Jan. 3, when it rose to 28 mm. Hg. On Jan. 4 tension was 40 mm. Hg. Miotics and acetazoleamide were prescribed. On Jan. 5 tension was 17 mm. Hg. On Jan. 7 tension was 17 mm. Hg. On Jan. 9 tension was 20 mm. Hg.

Comment.—There is every reason to think that the right eye will be protected permanently from angle closure glaucoma. In the left eye, if peripheral iridectomy had been done immediately after the tension was first reduced to normal with miotic treatment there is every reason to believe that the angle would have opened completely or nearly so and that the glaucoma would have been arrested. When the tension later rose in spite of miotic treatment, prompt operation might well have opened the angle sufficiently so that any residual glaucoma from permanent closure might well have been controlled medically. Under acetazoleamide therapy, though for some time the tension was controlled, more and more of the angle closed, until when surgical treatment was first undertaken the angle was almost completely closed by peripheral anterior synechias. The first operation failed to open the angle. Iridencleisis was followed by what appeared to be malignant glaucoma, though it was somewhat atypical in that the tension did not rise immediately after the operation, as is usually the case in malignant glaucoma. The outcome in the left eye is still uncertain. There is little evidence of filtration from the iridencleisis. At the moment, tension is controlled with miotics and acetazoleamide, but it is possible that further operation will be required. Indeed, the eye may be eventually lost in spite of further surgical attempts and medical treatment.

The outcome in the right eye illustrates again the great effectiveness of peripheral iridectomy if done early. The left eye illustrates the disastrous outcome which may ensue if one is lulled into a sense of security by the lowering of tension for a time with acetazoleamide, the angle is allowed to become completely and permanently closed by peripheral anterior synechias, and tension is high at the moment of operation.

REFERENCES

1. Becker, B.: Decrease in Intraocular Pressure in Man by a Carbonic Anhydrase Inhibitor, Diamox, Am. J. Ophth. 37:13-15, 1954.

2. Grant, W. M., and Trotter, R. R.: Diamox (Acetazoleamide) in the Treatment of Glaucoma, A. M. A. Arch. Ophth. 51:735-739, 1954.

Quantitation of Extraocular Muscle Innervation

GOODWIN M. BREININ, M.D., New York

Electrophysiologic approaches to the analysis of innervation in ocular motility have made evident the need for quantitative techniques.[1] That need has now been satisfied with the development of a full wave integrator and differentiator in one instrument. The former provides an integration of the energy developed in specific time intervals. The height of the condenser discharge is exactly proportional to the energy accumulated and discharged within these intervals. This discharge is fed into a second beam of the dual beam oscilloscope or can be written out on an ink writer. A simple linear measurement gives the desired information. The frequency response is from 5 to 1000 cps—a spectrum deemed adequate for electromyographic potentials.

The importance of this advance cannot be underestimated, since the evaluation of neuromuscular activity involves consideration of both amplitude and frequency. Inspection methods are inadequate to perform this task satisfactorily.

In addition, the differentiator provides an analysis of the slope changes in any given potential or run of potentials. These will not be considered in this paper.

The practical value of the technique of integration may be seen in the following studies.

A. Kinesiology

The levels of innervation of the extraocular muscles may be precisely compared as the eye rotates into the various fields of

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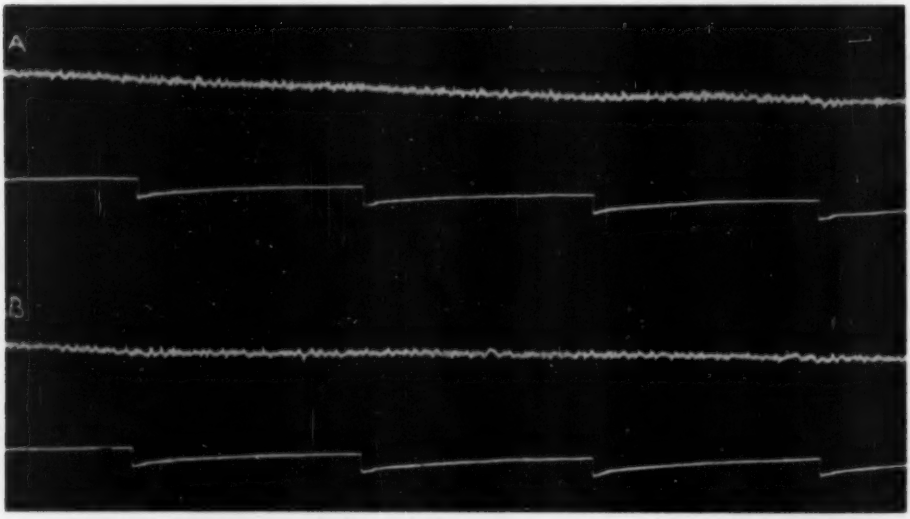

Fig. 1.—Electromyogram of right inferior rectus on horizontal versions; EMG above, integrator below. *A*, gaze right, no change; *B*, gaze left, no change.

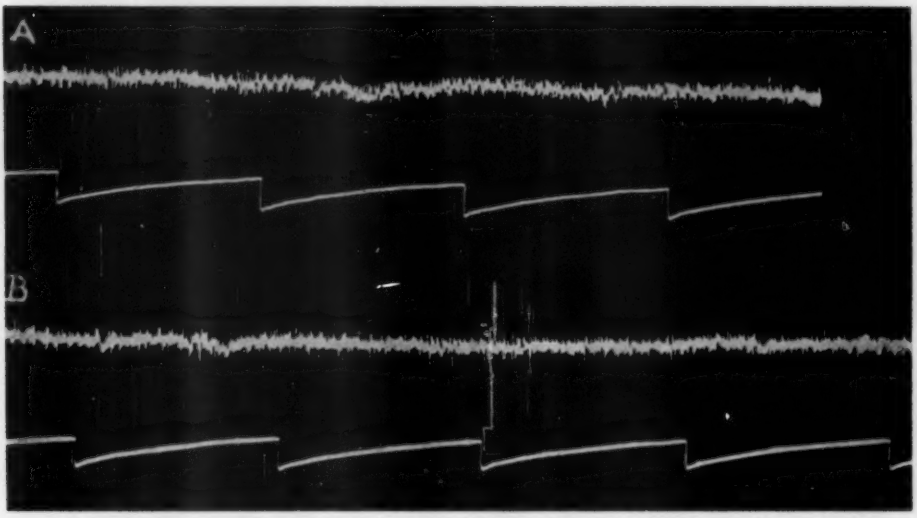

Fig. 2.—Electromyogram of left inferior oblique on horizontal versions. *A*, gaze right, no change; *B*, gaze left, no change.

gaze. This has demonstrated the inadequacy of some long-maintained concepts. There is no innervational basis for the belief that the vertical recti are active accessory adductors or the obliques active accessory abductors in horizontal rotations of the eye. In pure horizontal rotations the tonic activity of the vertical muscles (characterizing the primary position) does not significantly alter. They maintain a nearly constant level of discharge (Figs. 1 and 2). Whatever component of abduction or adduction may be manifested by the vertical obliques and recti will be a consequence of the relation of the muscle plane to the center of rotation of the globe. Thus, as the eye is adducted

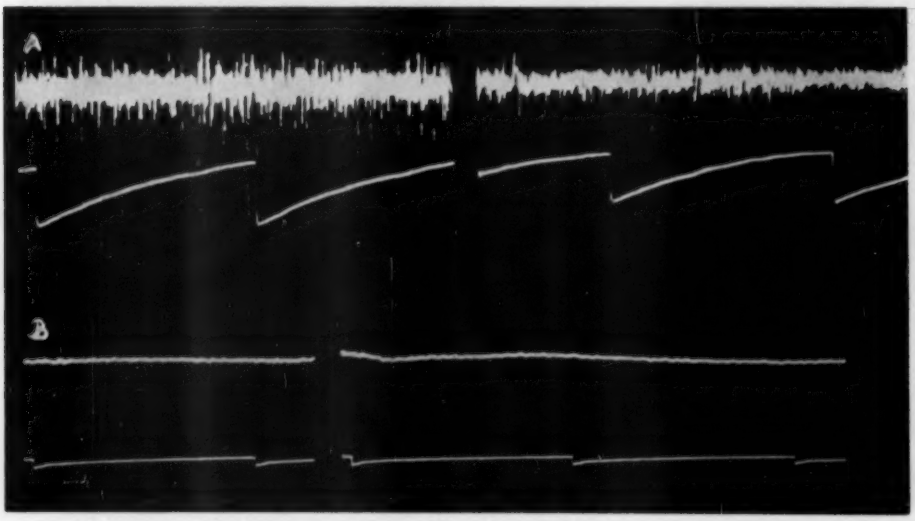

Fig. 3.—Electromyogram of right superior rectus; fields of gaze. *A*, left, up and out; right, up and in. *B*, left, down and in; right, down and out.

by the medial rectus the obliques balance each other vertically. The vertical recti, which also balance each other vertically, may develop a component of adduction owing to the change in the relation of their muscle plane to the center of rotation. But it is doubtful that this amounts to very much. When the eye rotates up, the superior rectus and inferior oblique both recruit, reaching a maximum when the eye attains its maximum excursion. The superior rectus attains its highest discharge with elevation in abduction (Fig. 3). Firing is usually slightly less with elevation in adduction. The inferior oblique is just the opposite (Fig. 4). The same features hold for the inferior rectus and superior oblique in depression. The vertical movers rapidly lose their innervation as the globe crosses the horizontal plane away from their field. Thus, in a tertiary position, e. g., up and out, the lateral rectus contracts while the medial rectus is inhibited; the superior rectus and inferior oblique contract while their opposite numbers are inhibited. There is hardly any alteration in discharge of the elevators with abduction or adduction so long as the eye is depressed. With sufficient depression they exhibit no firing at all (Figs. 3 and 4). This also holds for the depressors in elevation.

In monocular gaze straight up or down the horizontal recti also maintain a constant discharge level.

It should be pointed out that an accessory role of abduction for the obliques and adduction for the vertical recti is not denied but can be significant only when the globe has rotated into the torsional field of action of these muscles—and that only one vertical mover at a time can exhibit such a component, e. g., up and in for the superior rectus (accessory adduction). In any case,

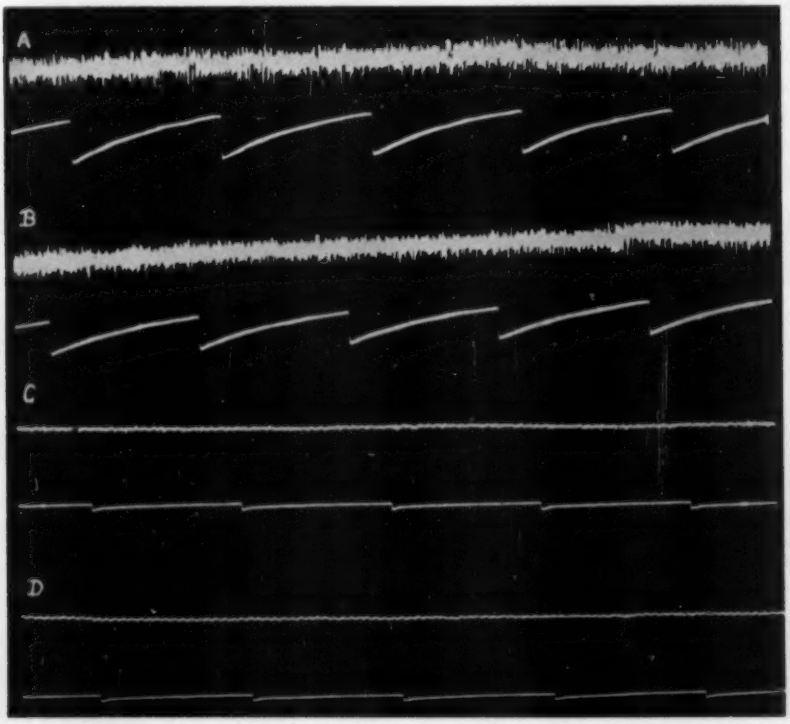

Fig. 4.—Electromyogram of left inferior oblique; fields of gaze. *A*, up and in; *B*, up and out; *C*, down and in; *D*, down and out.

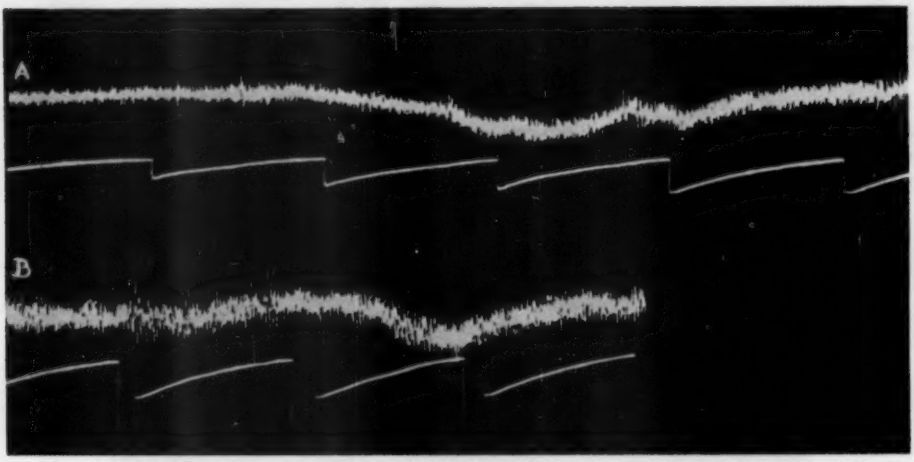

Fig. 5.—Electromyogram of left medial rectus. *A*, convergence up to the N. P. C.; *B*, dextroversion from the N. P. C.

it can occur only in consequence of the relation of its muscle plane to the center of rotation of the globe and is not due to a purposeful increase of innervation (which, if anything, is slightly less in this field).

The situation in convergence is interesting. It has been maintained that convergence is due solely to the action of the medial recti. The greater adduction of an eye in conjugate gaze, however, has been ascribed to the additional effect of the vertical recti acting as accessory adductors.[2] Electromyography demonstrates that when the near point of convergence (N. P. C.) has been attained and the gaze is directed to one side the additional internal rotation of

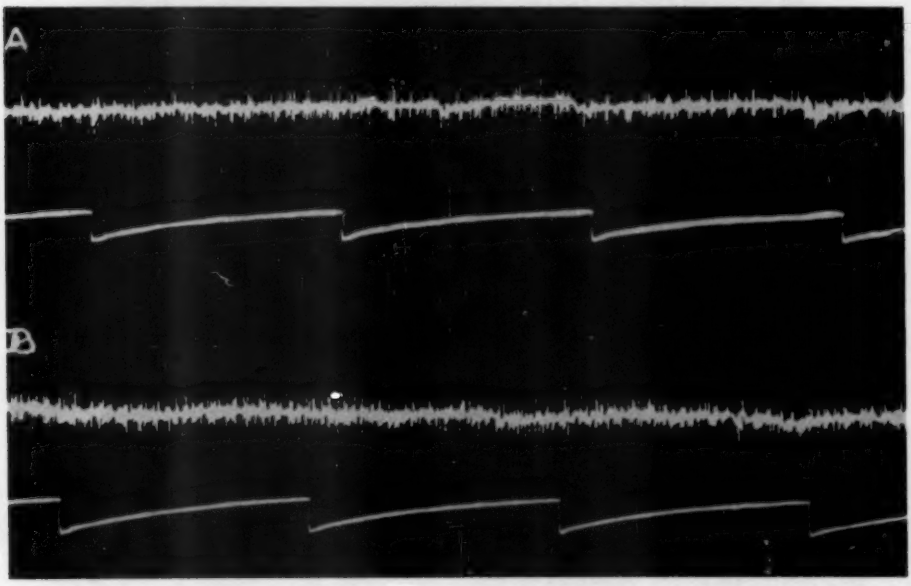

Fig. 6.—Electromyogram of left medial rectus (behind screen), showing accommodative convergence. *A*, no lens before fixing eye; *B*, —1 D. lens before fixing eye.

the adducted eye is due solely to markedly increased firing of its medial rectus (Fig. 5). The vertical recti maintain their usual tonic level. This indicates that the role of the vertical recti as accessory adductors is minimal and contributes no more, if at all, to version than to vergence.

It should be noted that a slight and variable recruitment on adduction was found in some subjects. This was usually due to excessive effort or electrode shift. The existence of real biological variation among subjects, however, does seem probable.

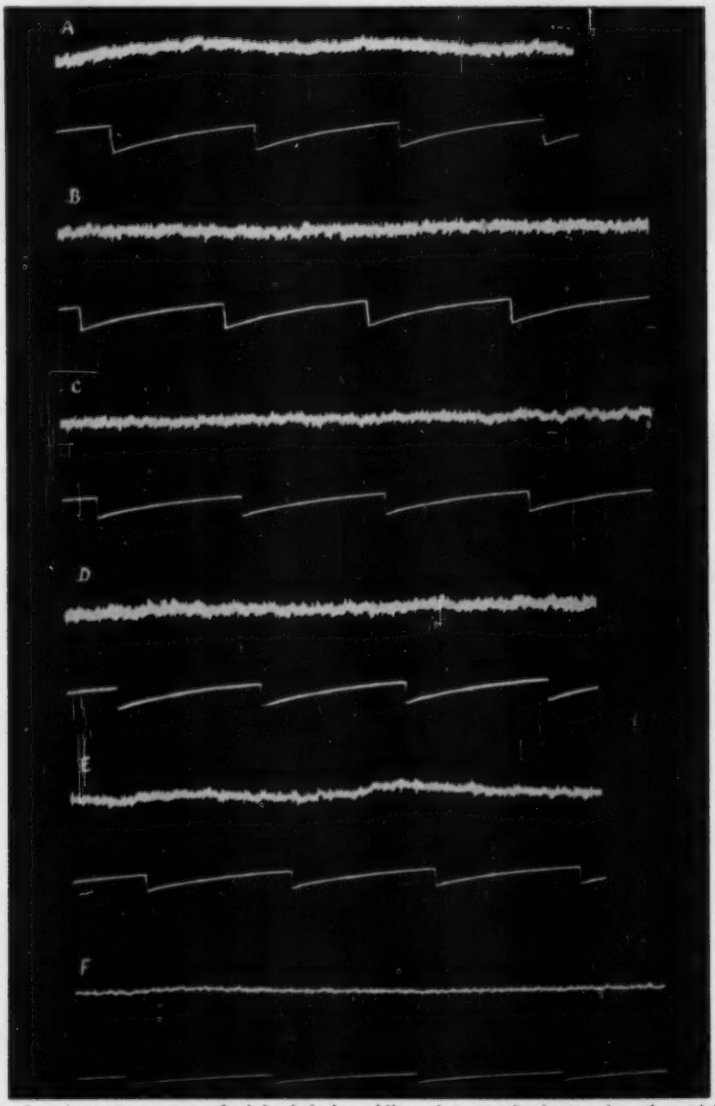

Fig. 7.—Electromyogram of right inferior oblique in myasthenia gravis. *A*, initial level. *B-F*, progressive fall-out of innervation over a three-minute period while attempting to hold eye in extreme elevation. There is a momentary recovery at *D* after a brief depression of the eye.

The inferior rectus, however, is actively firing during convergence below the horizontal plane. Its level of discharge is related not to convergence but to the degree of depression of the globe. But since intorsion is said to occur with convergence and not extorsion, its activity as an extorter must be overcome, presumably by the medial rectus acting as an intorter. This may be a function of the vertical level of convergence.

B. The Measurements of Lens- or Prism-Induced Innervation

The effect of a lens in augmenting or inhibiting accommodative vergence can be readily evaluated. The integrator discharge level permits exact quantitation of states of vergence whether spontaneous or induced. This is a most useful datum in the study of accommodation and convergence. Until now we have been forced to rely on the relative position of the two eyes in such studies. This method is essentially independent of the ocular movement effected. The interposition of graded increases of minus lenses before the fixing eye will elicit increasing amounts of accommodative vergence and hence increased levels of firing in the medial rectus of the nonfixing eye (behind a screen) (Fig. 6). This will not appear in the muscles of the fixing eye, for reasons that have been previously described.[3] * A comparison of innervation increments per diopter of lens power is thus achieved. The subject must look through the optical center of the lens to avoid prismatic effects. A ready comparison is also possible between lens-induced vergence in-

* When both eyes fix neither shows any change since accommodative convergence is negated by fusional divergence.

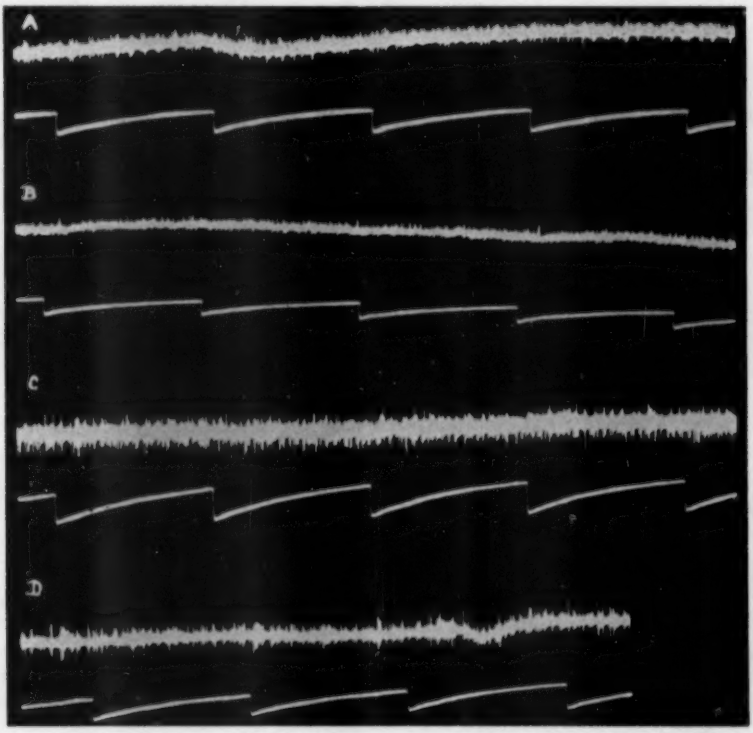

Fig. 8.—Electromyogram of right lateral rectus in myasthenia gravis. *A*, initial level; *B*, on protracted gaze right; *C*, 15 seconds after edrophonium was administered; *D*, 2 minutes after edrophonium was administered.

nervation and that due to linear distance of an appropriate accommodative symbol. Studies are in progress evaluating such changes in accommodative strabismus.

Fixation movement and fusional vergence induced by prisms are similarly quantitated in terms of innervation—this time recorded from the fixing eye behind the prism.

C. Evaluation of Drug Effects

A quantitative analysis of the action of drugs upon extraocular muscle innervation is simply achieved, providing a useful index to such effects. This is currently utilized in studies of myasthenia gravis. The characteristic myasthenic fall-out of innervation (Fig. 7) and the response to edrophonium (Tensilon) (Fig. 8) are readily measured.

Summary

Integration of electromyographic potentials permits exact quantitation of innervation. This has helped to clarify innervational aspects of the various positions of gaze, lens and prism deviations, and the effects of drugs upon the extraocular muscles.

550 First Ave. (16).

REFERENCES

1. Breinin, G. M.: Electromyography—a Tool in Ocular and Neurologic Diagnosis: I. Myasthenia Gravis, A. M. A. Arch. Ophth. 57:161, 1957.

2. Verhoeff, F. H.: Problems Concerning Convergence, Tr. Am. Acad. Ophth. 52:15, 1947.

3. Breinin, G. M.: The Nature of Vergence Revealed by Electromyography, A. M. A. Arch. Ophth. 54:407, 1955.

External Visibility of the Region of Schlemm's Canal

Report on a Family with Developmental Anomalies of Cornea, Iris, and Chamber Angle

HERMANN M. BURIAN, M.D.; M. HOBSON RICE, M.D., and LEE ALLEN, Iowa City

In a recent paper it was reported by Burian, Braley, and Allen [1] that the trabecular zone is externally visible by slit-lamp biomicroscopy in all normal eyes and that a thickening and prominence at the edge of this trabecular zone on the chamber side, constituting the so-called embryotoxon corneae posterius, is a relatively frequent occurrence. In no patient seen up to the time of publication of that paper could the region of the canal of Schlemm be identified in external examination. Ascher [2] had previously described a patient in whom the canal of Schlemm was visible owing to a coloboma of the corneoscleral limbus, but this case had remained unique. In the present paper we wish to report on two patients in whom we were able to observe the region of the canal of Schlemm by external slit-lamp examination and in whom we could verify this finding by gonioscopy. The two patients belonged to a family all of whose members presented, in varying degrees, one or more of the following signs: megalocornea, aplasia of the mesodermal leaf of the iris, miosis, corectopia, ectropion uveae, prominence of the ring of Schwalbe, persistent adherence of the iris to the tissues of the chamber angle, and pectinate ligament features. In other words, they presented varying degrees of the condition known as mesodermal dysgenesis of cornea and iris (Rieger [3]) or posterior marginal dysplasia of the cornea (Streiff [4]).

The family consisted of the father (Case 1), the mother (Case 2), and eight children ranging in age from 16 years to 11 months (Cases 3 to 10). All these we could examine. The family history was not very revealing. The father knew of no significant ocular disease in his parents or in his four sisters and two brothers or among his more distant relatives, except that one sister was nearsighted and was practically blind in one eye, this condition not being due to any known injury or diease. The mother's parents, one sister, and three brothers all had to their knowledge good eyes, but one of her maternal cousins had cataracts removed at a relatively early age and this man's son had to have both eyes removed for retinoblastoma.

So as to avoid a tedious reporting of each case, we have summarized the pertinent findings in all members of this family in Table 1 and listed the frequency of the occurrence of the salient features in Table 2.

We should have hesitated to report this family, since it does not add greatly to our knowledge of the symptom complex which they exemplify, if it were not for the new observations which we could make regarding the external visibility of the region of the canal of Schlemm. We shall, therefore, describe now in some detail our findings in the two patients in whom this observation was made.

The first is Case 6 (Table 1), an 11-year-old boy, who presented the following picture. His corneas were of normal size;

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From the Department of Ophthalmology, College of Medicine, State University of Iowa.

Presented by one of us (M. H. R.) at the Meeting of the Midwestern Section of the Association for Research in Ophthalmology, March 17, 1956, Chicago

TABLE 1.—*Findings in Members of Family with Various*

Case No.	Age, Yr.	Sex	Size of Horizontal Meridian of Cornea, Mm.	Intraocular Pressure, Mm. Hg.	Vision (Without Correction Unless Stated Otherwise)	Iris	Pupil	Trabecular Zone
1	45	M	R=L, 11.75	R=L, 14.6	R=L, 6/4.5−2	Blue, general mild atrophy	R=L, 3 mm.	Visible
2	39	F	R=L, 12.5	R, 14.6 L, 17.3	R=L, 6/6+3	Right, hazel; left, brown; no atrophy	R=L, 3 mm.	Well exposed
3	13	F	R=L, 13.0	R=L, 17.3	R, +4.50−0.75 ax 5=6/6−3 L, +6.50−3.50 ax 180=6/6−3	Brown; marked atrophy; pigment scattered over anterior surface; slight ectropion uveae O.U.	Extremely miotic (½ mm. or less); dilates only to 1.75 mm. with cyclopentolate; displaced upward and nasalward	Exposed
4	14	F	R=L, 11.75	R=L, 13	R=L, 6/6	Blue-gray; no atrophy	R=L, 5.5 mm.; slightly displaced upward and nasalward	Well exposed
5	12	F	R=L, 13.0	R=L, 17.3	R, +3.75−2.75 ×30=6/9−1 L, −2.00=6/60	Gray; marked atrophy	R=L, 3 mm.; displaced upward and nasalward	Widely exposed, especially on nasal side in O.S.; here texture clearly seen, fine pigment scattering
6	11	M	R, 11.5 L, 12.0	R, 13.0 L, 14.6	R, L.P. L, −0.25+ 1.00 ax 90= 6/9+4	Brown; mild atrophy	O.D., miotic (<1 mm.); O.S., miotic (2 mm.); O.U., displaced upward and slightly nasalward	Widely exposed; moderately heavy pigmentation of anterior trabecular zone temporally and below O.U.
7	8	M	R=L, 12.25	R=L, 17.3	R=L, 6/4.5	Brown-hazel, right slightly lighter than left; no atrophy, but very pronounced crypt formation	R=L, 5 mm.	Narrow exposure; no pigmentation
8	6	F	R=L, 13.0	R, 20.4 L, 17.3	R, −7.50=6/6 L, −10.50=6/6	Brown; left somewhat lighter than right; marked atrophy; slight ectropion uveae OS	Displaced upward and nasalward	Widely exposed; pigmentation of anterior trabecular zone temporally and below O.U.
9	2	F	R=L, 11.5	Not taken	R=L, useful	Brown; texture normal	Normal position and size	Average exposure; no pigmentation
10	1	M	R=L, 13.5	R=L, 20 (vinyl ether anesthesia)	Myopia (about −10.00 O.U.)	Atrophy of iris, demonstrated by retroillumination	Not noted	....

Degrees of Mesodermal Dysgenesis of Cornea and Iris

Slit-Lamp Biomicroscopic Findings			
External		Gonioscopic	Other Findings
Ring of Schwalbe	Region of Canal of Schlemm		
O.S. Possible mild prominence at 5 o'clock	Not identified	O.D. Some persistent adherence nasally; O.S. possible persistent adherence nasally of very thin portion of iris	----
Mildly prominent in lower nasal third of O.D. and lower temporal third of O.S.	Not identified	Prominent ring of Schwalbe in upper portion O.D., lower portion O.S.; fine broken and bridging iris processes	----
Prominently visible nasally and temporally in O.D., only temporally in O.S.; pectinate fibers attaching to it in O.D.	Not identified	Iris bows backward in periphery; heavy pigmentation of Schlemm's canal where visible; iris processes adherent to trabecular zone; iris adherence covering most of trabecular zone in temporal region	----
Slightly prominent temporally in O.D.	Assumed to be identified in O.D. as dense tissue peripheral to ring of Schalbe and trabecular zone; no pigmentation	Angles open; ring of Schwalbe prominent temporally and inferiorly in O.S., in spots in O.D.; no pigmentation of trabecular zone or region of Schlemm's canal	----
Marked prominence on nasal and temporal side O.U., scalloped, with patches of pigment; broad areas of persistent adherence of iris to ring temporally, small adherence nasally	Not identified	Iris bows backward in region of zonule; angle wide open above and below; prominent ring of Schwalbe, especially nasally, seen in O.U.; also in O.U. iris temporally adherent to ring of Schwalbe for distance of 3-4 mm.; nasally only halfway up trabecular zone for distance of 2 mm.; region of Schlemm's canal tannish color	Left exotropia: 12△ for distance 25△ for near
No prominence	Identified by dense pigmentation on lower temporal side of limbus in each eye, more pronounced in O.D.	Iris bowed backward in region of zonule; atrophic; pigment scattered on anterior portion of trabecular zone; region of canal of Schlemm heavily pigmented; scleral spur recognized; numerous bridging iris processes; no prominent ring of Schwalbe; persistent adherence of iris from 6-7 o'clock in O.S., similar adherence in temporal angle	Dense congenital cataract O.D.; lens appears to be subluxated; numerous punctate opacities in lens O.S.; right esotropia of 45 degrees
Prominent in O.D. from 2 to 4 o'clock; in O.S. from 8 to 10 o'clock	Not identified	Numerous bridging iris processes, going to scleral spur; pearliness of Schwalbe's ring here and there; prominence at 1 o'clock in O.S., at which point club-shaped bridging pectinate strand inserts below ring; no pigmentation of trabecular zone	----
No prominence	Identified by very heavy pigmentation on lower temporal side of limbus, especially in O.D.	No prominence of ring of Schwalbe; pigment scattered on anterior portion of trabecular zone; very heavy pigmentation of region of Schlemm's canal; scleral spur identified; broad ciliary body band seen below	Fine strand-like remnants of pupillary membrane in O.D.
No prominence	Not identified	Not done	----
----	Not identified	Attempted in anesthesia with little success as to observation of details; definitely no pigment in trabecular zone in either eye	----

TABLE 2.—*Frequency of Occurrence of Salient Features of Mesodermal Dysgenesis of Cornea and Iris in One Family*

Condition			No. in Family Showing Trait
Megalocornea (horizontal diameter >12 mm.)			6
Iris atrophy			5
Pupil	Miotic		3
	Displaced		5
Ring of Schwalbe recognized	In external view	Prominent	4
		Not prominent	2
	In gonioscopic view	Prominent	5
		Not prominent	1
Persistent iris adherence			4
Pectinate ligament features			4
Pigmentation of anterior trabecular zone recognized.	In external view		2
	In gonioscopic view		4
Pigmentation of region of canal of Schlemm recognized.	In external view		2
	In gonioscopic view		3

the irises were brown and showed a mild atrophy of the mesodermal layer. The pupils were round but miotic and were displaced upward and nasalward. Slit-lamp examination of the limbal area revealed a widely exposed trabecular zone, the corneal edge of which faded into the clear corneal tissue without prominence of the ring of Schwalbe. Thus far, the boy presented only a mild atrophy of the iris and miotic displaced pupils. Iris atrophy of varying degree was noted in five members of the family; a pronounced miosis, in three, and a displacement of the pupil, again, in five. The typical picture of the condition is reproduced in Figure 1, which shows the left eye of Patient 3, with iris atrophy, miotic displaced pupil, slight ectropion uveae, and pigment scattering on the anterior surface of the iris. In addition, this patient had megalocornea and a mildly prominent ring of Schwalbe at the corneal edge of the well-exposed trabecular zone.

The most important finding, present in both eyes of Patient 6, was a moderately heavy scattering of pigment on the trabecular zone adjacent to its corneal edge visible by slit-lamp examination and very heavy pigmentation peripheral to it at the limbus (Fig. 2). We interpreted this to be a pig-

Fig. 1 (Case 3).—Left eye. Iris atrophic. Pupil miotic and displaced. Prominent ring of Schwalbe (Schw.) nasal side.

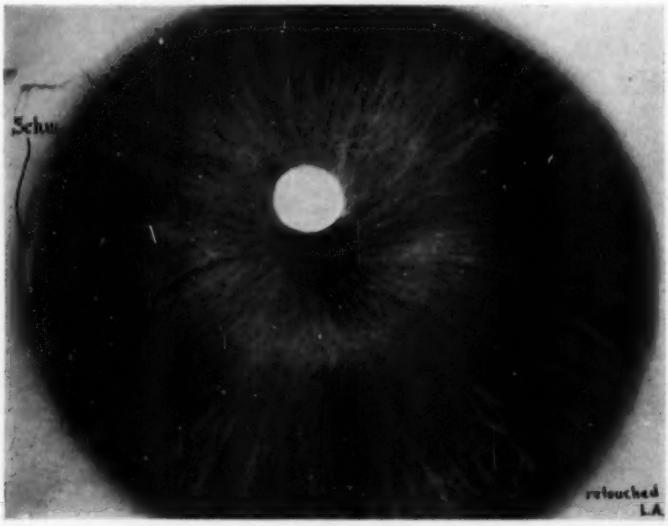
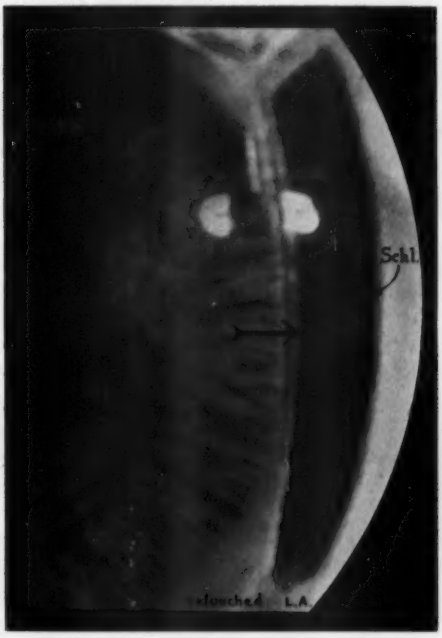


Fig. 2 (Case 6).—Lower temporal region of limbus of left eye, showing scattering of pigment on anterior trabecular zone and heavy pigmentation of region of Schlemm's canal (*a*), visible in external slit-lamp examination.

mentation of the region of the canal of Schlemm, and our assumption was confirmed by gonioscopic examination. This showed a bowing backward of the atrophic iris in the region of the zonule; pigment was scattered on the anterior portion of the trabecular zone, and the region of Schlemm's canal was heavily pigmented. We could orient ourselves in the angle by the scleral spur, which was clearly recognized. There were also numerous bridging iris processes, but the line of Schwalbe was nowhere prominent. In Figure 3 a photograph of the temporal angle of the right eye is reproduced which shows some of the features mentioned. A particularly noteworthy feature was a persistent adherence of the iris to the region of the canal of Schlemm in the left eye between 6 and 7 o'clock. This persistent adherence, the iris atrophy, and the pigment distribution on the trabecular zone are clearly demonstrated in the drawing reproduced in Figure 4. A similar persistent adherence of the iris, but in this case to Schwalbe's ring, in the temporal angle of the left eye of another member of this family (Case 5, Table 1), is represented in Figure 5.

Fig. 3 (Case 6).—Photograph of temporal angle of right eye, showing adherence of iris to trabecular tissue and heavy pigmentation of area of Schlemm's canal (Schl.).



Patient 8, a 6-year-old girl, presented a situation similar to that of her older brother. She did, however, have a pronounced megalocornea, as did five other members of the family; marked iris atrophy, and a displaced pupil, but, again, no prominent ring of Schwalbe. In external examination pigment was found scattered on the anterior portion of the widely exposed trabecular zone in parts of the limbus, and the region of the canal of Schlemm was identified by

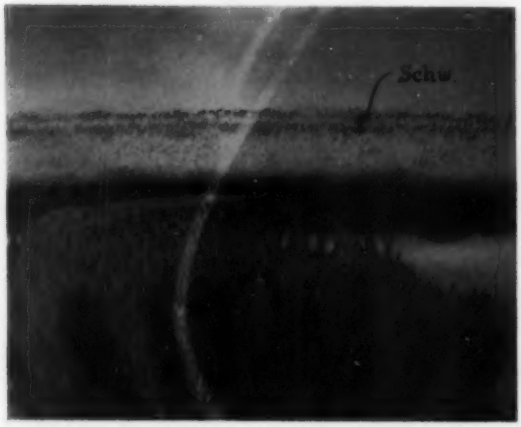
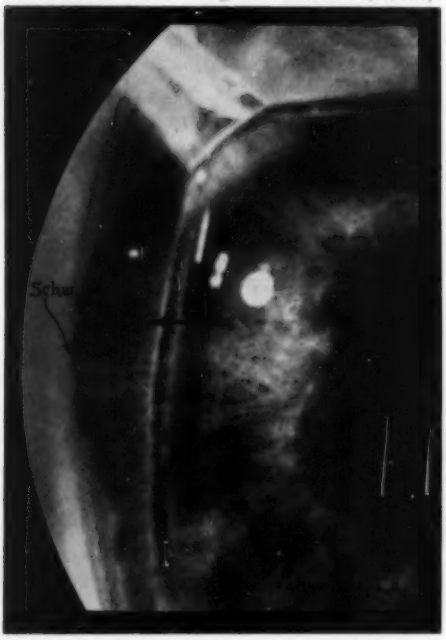


Fig. 4 (Case 6).—Lower angle of left eye. Pigment at anterior border of trabecular zone (Schw.); heavy pigmentation of the area of Schlemm's canal. No prominence of Schwalbe's ring. Persistent adherence of iris to lower part of trabecular zone.

very heavy pigmentation. Gonioscopic examination permitted us to confirm this identification (Fig. 6). In one of the patients (Case 3, Table 1) a heavy pigmentation of the area of Schlemm's canal was seen gonioscopically, but not in external examination. The trabecular zone was exposed to an average width and there was a prominence of the ring of Schwalbe, but the external limbus extended too far corneaward to permit visualization of the area of Schlemm's canal.

Fig. 5 (Case 5).—Photograph of temporal angle of left eye. Iris atrophic; broad area of persistent adherence of iris to ring of Schwalbe (Schw.).



Having become aware of the fact that the region of the canal of Schlemm may be accessible to external inspection by slit-lamp examination, we paid particular attention to this possibility in other patients and have noted in certain instances in which the anatomic conditions were favorable a dense tissue of texture similar to the anterior trabecular zone, situated peripherally to the ring of Schwalbe and the anterior trabecular zone. We have assumed this to be the area of the canal of Schlemm. Such was the case in Patient 4 (Table 1) of the family under discussion. We could make this identification with more assurance in another patient, a 20-year-old girl not belonging to this family. In this patient there was a definite "coloboma" of the external limbus on the nasal side of each eye. In most persons the horizontal meridian of the external limbus extends less far corneaward than in other areas of the sclerocorneal limbus and may occasionally recede so far scleraward that the impression is gained that a small semilunar piece of sclera is missing and the structures of the chamber angle become widely exposed to external examination. One is then entitled to speak of a "coloboma of the external corneoscleral limbus," as did Kraupa [5] and

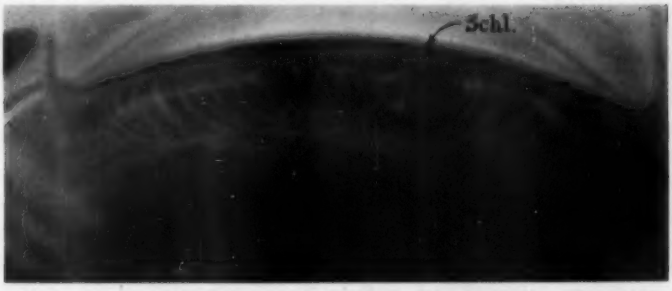
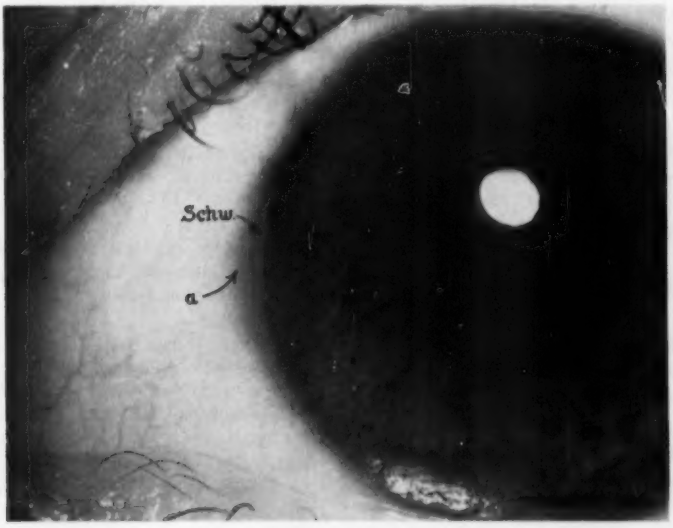


Fig. 6 (Case 8).—Photograph of lower angle of right eye. Heavy pigmentation of the region of Schlemm's canal (Schl.).

Ascher.[2] This situation obtained in the 20-year-old patient to whom we have just referred. The nasal half of her left eye is shown in Figure 7. The patient had no ocular complaint other than a hordeolum on the left upper lid. The uncorrected vision was better than 6/6 in each eye, and there were no demonstrable pathologic changes in the media and fundi of her eyes. However, there was the coloboma of the corneoscleral limbus on the nasal side of each eye, and external slit-lamp examination revealed a prominent ring of Schwalbe in that area and a tag of a pectinate strand inserted on the ring at 3 o'clock in the right eye. Peripherally to the ring the trabecular tissue was seen, and peripherally to it, and continuous with it, a denser tissue interpreted by us to be the area of the canal of Schlemm. Since we noted no pigmentation of this area, we attempted to fill the canal itself with blood by compression of the jugular vein, hoping to identify it in external examination, but we did not succeed in doing so. By gonioscopy we found an angle of average width with an acute apex. The ring of Schwalbe was prominent in the nasal angle in an area of about 4 mm. in

Fig. 7.—Photograph of nasal half of left eye of a 20-year-old woman with coloboma of the corneoscleral limbus. There is a prominent ring of Schwalbe (Schw.). The denser tissue (*a*) at the limbus at 9 o'clock corresponds to the area of the canal of Schlemm as seen by gonioscopy. This patient had no pigmentation of the trabecular zone.



length; neither the anterior trabecular zone nor the region of Schlemm's canal showed any pigmentation. In all four quadrants of both eyes there were iris processes in the form of pectinate ligament strands going across the scleral spur and inserting low on the trabecular zone. The tag of pectinate ligament strand seen in the right eye on external examination inserting on the ring of Schwalbe at 3 o'clock was identified in gonioscopy. It did not continue back to the iris but appeared to be broken off.

Returning now to the family of patients reported in this paper, it is of interest to comment on two additional observations. One pertains to the relationship of megalocornea to refractive errors. As will be seen from Table 1, the patients (Cases 3, 5, 8, and 10) with pronounced megalocornea all had significant errors of refraction, but there was no consistency in type or amount. Two patients (Cases 8 and 10) had high spherical myopic errors; two had a high hyperopic astigmatism (Cases 3 and 5). One of the last two had an antimetropia. In one of the four patients the visual acuity could not be determined; two had normal visual acuity, and one (Case 5) had slightly subnormal vision in the right eye, with the hyperopic astigmatism, but the myopic left eye was deeply amblyopic.

The second observation relates to the intraocular pressure in these patients. All tension measurements—and most of these were done repeatedly—indicated normal intraocular pressure in all patients, even in those who showed by external or gonioscopic examination a heavy pigmentation of the region of the canal of Schlemm. Although none of the children had congenital glaucoma, the patients will remain under observation to check on the possible development of juvenile glaucoma. One is justified in concluding that the observed anomalies as such do not lead to development glaucoma. They may, however, be a predisposing factor in the production of juvenile glaucoma if other factors concur to disturb the equilibrium of production and outflow of aqueous.

Summary

The ocular findings in a family of 10 members are described. All of them had in varying degree one or more of the following congenital anomalies of the anterior segment of the eyes: megalocornea, aplasia of the mesodermal leaf of the iris, miosis, corectopia, ectropion uveae, prominence of the ring of Schwalbe, persistent adherence of the iris tissue to the chamber angle, and pectinate ligament features.

In two members the region of the canal of Schlemm was heavily pigmented and could be identified in external examination. It is pointed out that this identification can also be made in the absence of pigmentation where the anatomic conditions are such that the external limbus does not extend as far corneaward as is ordinarily the case. In support of this statement there is included in this paper the description of the findings in one patient, not a member of the same family, who had a definite coloboma of the external scleral limbus.

Department of Ophthalmology, College of Medicine, State University of Iowa.

REFERENCES

1. Burian, H. M.; Braley, A. E., and Allen, L.: Visibility of the Ring of Schwalbe and the Trabecular Zone: An Interpretation of the Posterior Corneal Embroyotoxon and the So-Called Congenital Hyaline Membranes on the Posterior Corneal Surface, A. M. A. Arch. Ophth. 53:767-782 (June) 1955.

2. Ascher, K. W.: Partial Coloboma of the Scleral Limbus Zone with Visible Schlemm's Canal, Am. J. Ophth. 24:615-619 (June) 1941.

3. Rieger, H.: Beiträge zur Kenntnis seltener Missbildungen der Iris: II. Über Hypoplasie des Irisvorderblattes mit Verlagerung und Entrundung der Pupille, von Graefes Arch. Ophth. 133:602-635, 1935.

4. Streiff, E. B.: Dysplasie marginale postérieure de la cornée (embryontoxon posterius Axenfeld) dans le cadre des malformations irido-cornéennes, Ophthalmologica 118:315-827 (Oct.-Nov.) 1949.

5. Kraupa, E.: Fehlen des Lederhautbandes in Sichelform als Abweichung vom gewöhnlichen Verhalten der Hornhaut-Lederhautgrenze, Klin. Monatsbl. Augenh. 64:698-700, 1920.

Effects of Intravenous Urea on Intraocular Pressure in the Monkey

RICHARD P. BUNGE, M.S.; R. CLARKE DANFORTH, B.S., and PAUL H. SETTLAGE, Ph.D., M.D., Madison, Wis.

The osmotic relationship between blood and aqueous humor is a factor of well-recognized importance in governing intraocular pressure.[1] The aqueous is slightly hypertonic to blood.[2-4] Friedenwald[5] and Kinsey[6] postulate that the hypertonicity of the aqueous derives from the formation of an excess of hydroxyl ions, which, in reacting first with carbon dioxide and then with sodium and other cations, maintains the ionic concentrations of the aqueous above plasma levels. The rate of aqueous flow is considered to be a function of this osmotic relationship.

Osmotic changes in the blood may alter aqueous flow.[7] Many osmotic agents, especially sugars, have been used for the purpose of influencing intraocular pressure. Hertel,[8] in 1914, demonstrated that urea reduced intraocular pressure when injected intravenously in the rabbit. In an experimental study, Fremont-Smith and Forbes[9] have shown that intracranial and intraocular pressures are closely related and that they react in parallel to many systemic influences, e. g., thoracic pressure, jugular compression, and intravenous water injection. According to these investigators, urea produces a symmetrical reduction of intracranial and intraocular pressure in rabbits, dogs, and monkeys. In this report, which appeared in 1927, they suggested that urea might prove to be of clinical value.

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From the Department of Anatomy of the University of Wisconsin Medical School.

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This suggestion was first followed in 1956, when Javid and Settlage[10] demonstrated that urea is more effective than sucrose or glucose in reducing intracranial pressure in man. This clinical work had been preceded by animal experimentation.[11] Urea was shown to be superior to the sugars, not only in degree of tension reduction, but also in duration of effect. Further reports[12,13] suggest a variety of applications for the use of urea in the control of intracranial edema and supplement the larger body of literature concerning its use as a diuretic.

The recent successful use of urea to reduce intracranial pressure in man, and the demonstrated parallelism between intracranial and intraocular pressure, provided the stimulus for the present systematic study of the effect of this drug on intraocular pressure. This report compares the effect of hypertonic urea with that of hypertonic sucrose and dextrose, as well as with the recently developed agent for reducing carbonic anhydrase activity, acetazoleamide (Diamox).

Materials and Methods

The experimental animals were seven Macaca mulatta monkeys weighing between 4.15 and 7.6 kg. Anesthesia was induced by the intramuscular injection of 42 mg/kg. of freshly dissolved pentobarbital (Nembutal). Intramuscular injection of about one-fourth the initial dose every 80 to 90 minutes maintained an adequate level of anesthesia. The animals were placed in the supine position, eyes directed upward, with the head cradled in towelling. In the initial experiments an ophthalmic ointment (butacaine

[Butyn] sulfate [2%] and nitromersol [Metaphen] [1:3000]) was applied to allow lighter general anesthesia. When experience revealed that the ointment did not provide any advantages in this regard, its use was discontinued.

Pressure measurements were made with the McLean tonometer. Left and right eyes were studied separately, and the results are separately reported. The curves in the Figures chart pressures for only one eye. Readings from the McLean tonometer scale, which is calibrated in millimeters of mercury of intraocular pressure for the human eye, were used in this study as an index of relative changes rather than as a true measure of intraocular pressure. It was found that the instrument could be used in the monkey with a high degree of confidence. In special control studies in which two experimenters made independent observations, the disparity between readings was rarely greater than two divisions of the tonometer scale.

Tonometer readings were taken every half-hour during an experimental period lasting 10 to 12 hours. In each of the seven animals the intraocular pressure was measured during a 12-hour control period without the administration of any drug other than the anesthetic. This control experiment was designed to indicate the individual reactions to prolonged pentobarbital anesthesia as well as to repeated tonometer applications. All experiments were begun between 7.00 and 9:00 a. m.

All drugs (excluding pentobarbital) were administered intravenously in the short saphenous or the medial cubital vein. The hypertonic solutions were administered at a rate of 2.5 to 3.0 cc. per minute. Commercial preparations of sucrose, dextrose, and acetazoleamide were used. Urea solutions were prepared in the following manner: The urea was weighed on clean filter paper, transferred to a sterile graduate, and made up to correct volume with sterile 5% dextrose solution. The urea dissolved with a negative heat of solution and was allowed to warm to room temperature before injection. Only freshly dissolved urea was used.

The following doses were used:

Dextrose	2.5 gm/kg. (5 cc/kg. of 50% solution)
Sucrose	2.5 gm/kg. (5 cc/kg. of 50% solution)
Acetazoleamide	50 mg/kg. (0.5 cc/kg. of 10% solution)
Urea	0.75 gm/kg. (2.5 cc/kg. of 30% solution)
Urea	1.5 gm/kg. (5.0 cc/kg. of 30% solution)
Urea	2.5 gm/kg. (5.0 cc/kg. of 50% solution)

In two monkeys the dose of 2.5 cc/kg. of 30% urea was repeated when the pressure returned to normal. Except in the case of urea, the doses were considerably higher (7 to 10 times) than the average dose per kilogram in man as given in a standard pharmacology text.[14] Urea has been administered to man in amounts equivalent to those used in the present study, i. e., 1.5 gm/kg.[12]

Results

Normal Intraocular Pressure in the Monkey.—During 29 two-hour control periods in seven monkeys the exact mathematical average of 145 readings for the right eye was 26.042; for the left, 26.057. The lowest average control pressure was 20.6; the highest was 30.4. These data indicate that the average normal intraocular pressure in seven Macaca mulatta monkeys, determined in 290 separate readings, was approximately 26 scale units of the McLean tonometer, with a range between 20 and 30 scale units in the various animals.

Control Experiments.—Effect of 10- or 12-hour periods of pentobarbital anethesia on intraocular pressure: The pressure curves obtained during the control experiments, in which no drug was administered, can be divided into three types. In two animals the pressure varied only slightly over a 12-hour control period during which pressure measurements were made every one-half hour (See Fig. 2). In a second group (two animals) the pressure showed a gradual decline of 7 to 9 tonometer scale units during the 10-hour control period, as illustrated in Figures 1 and 3*B*. In the third group (three animals) the curves fell off sharply after a comparatively steady six-hour period. After this initial plateau there was a fall of 10 to 15 scale units during the subsequent six hours.

TABLE 1.—*Decrease in Intraocular Pressure Following Intravenous Injection of Acetazoleamide and Various Hypertonic Solutions* *

Monkey No.	Eye	Normal Intraocular Pressure†	Decrease in Intraocular Pressure†					
			Dextrose 50% (5 Cc./Kg.)	Sucrose 50% (5 Cc./Kg.)	Acetazoleamide (50 Mg./Kg.)	Urea 30% (2.5 Cc./Kg.)	Urea 30% (5 Cc./Kg.)	Urea 50% (5 Cc./Kg.)
87	O.D.	28.1		7.2	3.8	5.2	19.4	18.5+
	O.S.	27.4		7.2	2.6	6.4	20.4	16.5+
92	O.D.	24.3			6.2			
	O.S.	24.6			5.2			
94	O.D.	29.6		11.0	6.4	15.8	21.0+	
	O.S.	28.9		7.8	6.8	17.0	20.2+	
96	O.D.	25.5		6.0	5.4		9.5+	
	O.S.	24.9		4.7	5.6		8.9+	
101	O.D.	28.1	6.4				16.0+	18.8+
	O.S.	28.3	8.3				17.2	18.2+
102	O.D.	22.8	3.0				12.7+	11.4+
	O.S.	22.8	4.8				11.2+	13.8+
103	O.D.	23.9	6.2				11.4+	14.4+
	O.S.	25.5	6.8				14.0+	16.0+
	Av.		5.9	7.3	5.8	11.1	15.2+	15.9+

* The values given for normal intraocular pressure were obtained by averaging all the control period readings for the individual animal. The degree of pressure change was calculated by subtracting the lowest reading following drug injection from the average of the control readings of the particular experiment. The plus values in the last two columns of the table indicate that the pressure fell below 10, which is the lowest value on the tonometer scale. In many of these instances the pressure decreases were undoubtedly substantially greater than the indicated value.
† The pressure values are in scale units of the McLean tonometer.

In three animals (Monkey 92 and two animals not included in the present series) the control experiment was varied in an attempt to determine whether the application of the tonometer every 30 minutes might itself be responsible for a gradual pressure drop over a 10- or 12-hour period. In these animals pressures were taken every one-half hour on the right eye but only every six hours on the left eye. These three experiments indicated that tonometer massage was not responsible for the gradual fall in intraocular pressure when the pressure was measured repeatedly for long periods of time; the readings for left and right eyes never diverged more than 2 to 3 scale units.

Results of Drug Administration.—The results are summarized in Tables 1 and 2. As seen in Table 1, the intravenous injection of urea in any of the three dosages tested produced substantially greater reductions in intraocular pressure than did dextrose, sucrose, or acetazoleamide. The effect of 5 cc/kg. of 30% urea was more than twice as great as the effect of any of these three drugs. This corresponds well with the findings of

TABLE 2.—*Duration of Drop in Intraocular Pressure Following Intravenous Injection of Acetazoleamide and Various Hypertonic Solutions* *

Monkey No.	Eye	Normal Intraocular Pressure	Duration of Drop in Intraocular Pressure, Min.					
			Dextrose 50% (5 Cc./Kg.)	Sucrose 50% (5 Cc./Kg.)	Acetazoleamide (50Mg./Kg.)	Urea 30% (2.5 Cc./Kg.)	Urea 30% (5 Cc./Kg.)	Urea 50% (5 Cc./Kg.)
87	O.D.	28.1		60	60–90	75–90	----†	270
	O.S.	27.4		60	60–90	75–90	----†	270
92	O.D.	24.3			110			
	O.S.	24.6			80			
94	O.D.	29.6		80	60–120	120	180	
	O.S.	28.9		80	120	120	180	
96	O.D.	25.5		110	110		100+†	
	O.S.	24.9		110	110		100+†	
101	O.D.	28.1	60				170–200	240
	O.S.	28.3	60				170–200	240
102	O.D.	22.8	30				180	330
	O.S.	22.8	30				180	330
103	O.D.	23.9	30				----‡	240
	O.S.	25.5	30				180	240
	Av.		40	83	96	101	163	270

* The values for the duration of the period of pressure decrease were obtained by determining the interval between the time when the pressure first began to fall following drug administration and the point of leveling off of the postinjection pressure curve. By plotting the results of each experiment separately, it was possible to locate these points on the curve accurately.
† Experiment terminated before duration of drop could be accurately determined.
‡ The right eye did not return to normal but stayed below 10(mm. Hg) for the remainder of the experimental period.

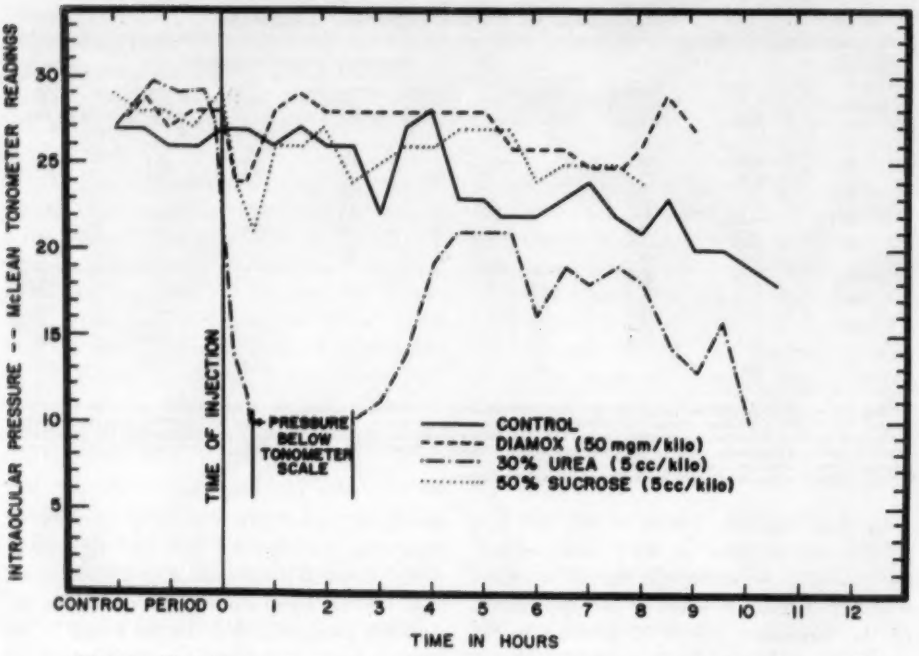

Fig. 1.—The effects of acetazoleamide, urea, and sucrose on intraocular pressure in Monkey 87.

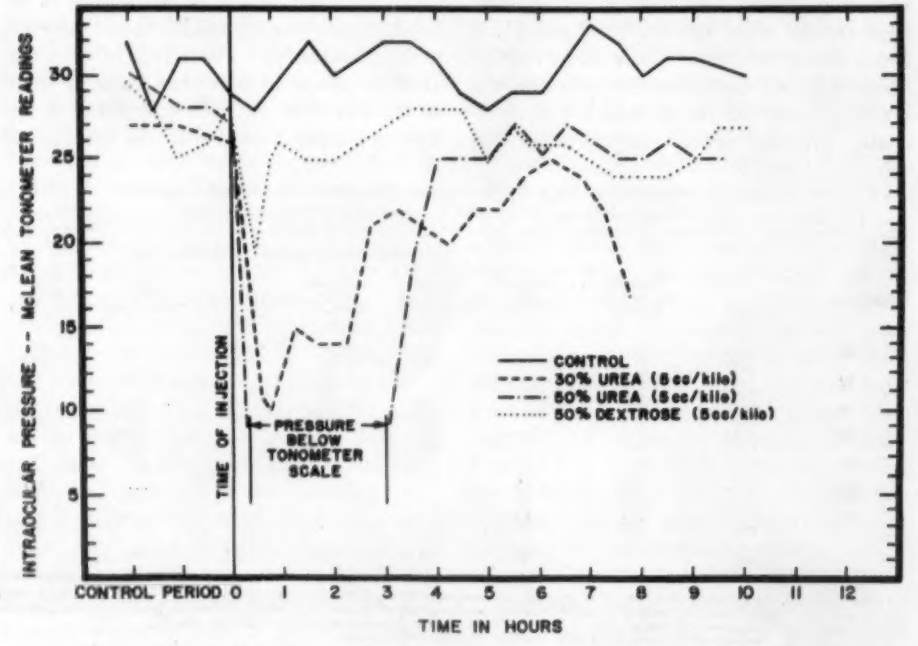

Fig. 2.—The effects of urea and dextrose on intraocular pressure in Monkey 101.

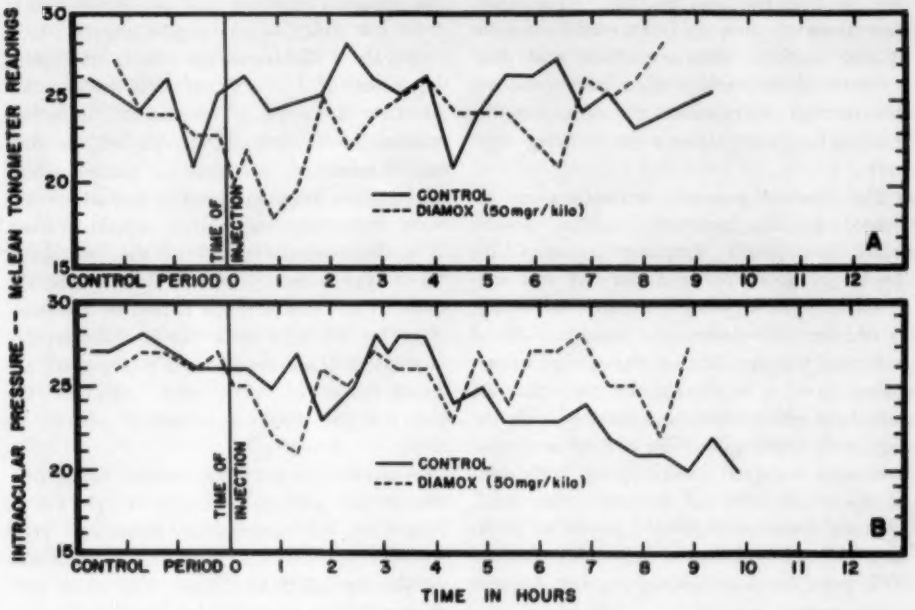

Fig. 3.—The effects of acetazoleamide on intraocular pressure in Monkeys 92 (*A*) and 96 (*B*).

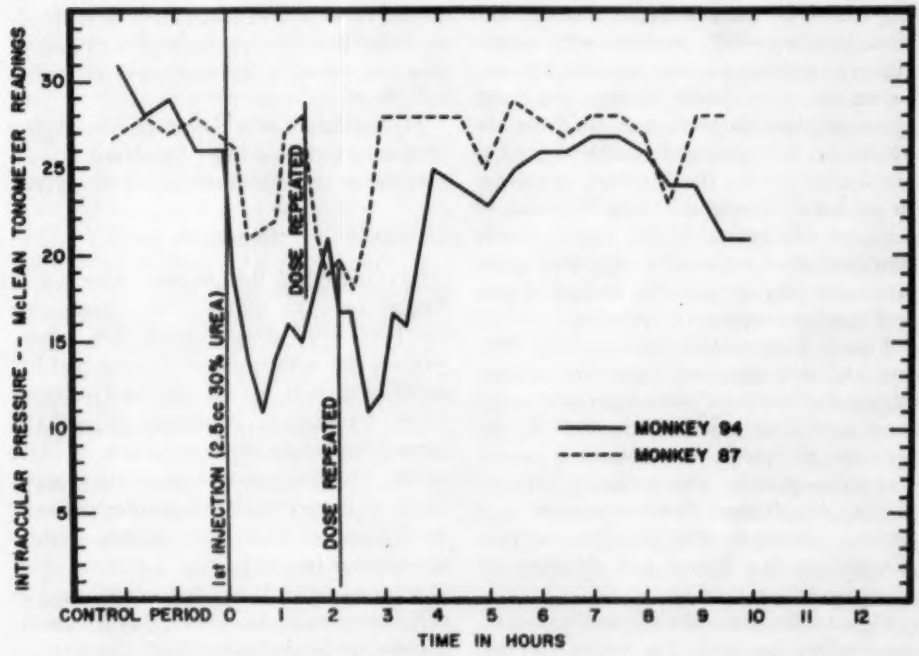

Fig. 4.—The effects of repeated urea injections on intraocular pressure in Monkeys 94 and 87.

Smythe, Smythe, and Settlage [11] regarding the effects of urea on intracranial pressure in the monkey. Acetazoleamide and dextrose are about equally effective in reducing the normal intraocular pressure in the monkey; sucrose causes a somewhat greater drop.

The marked pressure reductions, as indicated by the tonometer readings, were easily detectable by simple palpation. With the larger doses of urea the eye was rendered *breiweich* (completely soft to touch), to use the expression of Hertel.[8] Table 2 indicates the duration of the period of reduced pressure. Except in the case of acetazoleamide, this varied directly with the degree of depression. The return to normal pressures occurred most rapidly with dextrose, which affected pressure the least, whereas the most prolonged period of pressure reduction followed administration of 50% urea, the solution causing the greatest pressure drop.

Figures 1 to 4 illustrate the results in graphic form. Figure 1 is a comparison of the effects of acetazoleamide, sucrose, and urea in Monkey 87, together with control readings over a 10-hour period. The experiments were spaced at least one week apart to allow complete recovery from the effects of the prolonged anesthesia. It is interesting to note the excellent agreement in pressures during the respective control periods. The curves in this Figure clearly illustrate the superiority of urea over acetazoleamide and sucrose, in both degree and duration of pressure reduction.

Figure 2 compares dextrose with 30% and 50% urea solutions. Again the readings during the two-hour control periods are in good agreement, especially in view of the fact that the curves were obtained over a four-week period. The pressure dropped sharply in each case. Dextrose was the least effective substance; 50% urea was the most effective in the degree and duration of pressure change.

Figure 3 illustrates the effect of acetazoleamide in two monkeys. The results were not striking (5.2 to 6.2 tonometer units), though the duration of effect was somewhat greater than for either of the sugars tested.

Figure 4 illustrates the effects of repeating a dose of 2.5 cc/kg. of 30% urea in each of two monkeys. The second injection, administered when the effects of the first had diminished, produced a change which was at least as pronounced as that which was seen following the initial administration. The durations of effect of the two doses were approximately equal. By dividing the dose in this manner, the period of action of 5 cc/kg. of 30% urea can be considerably increased. This suggests that repeated administration of urea may maintain the lowered pressure for extended periods of time.

Administration of the various drugs produced no adverse effects, except for a transient hemoglobinuria following 50% urea. This did not seem to impair the health of the animal in any way. The same phenomenon was observed by Smythe et al. in a study on monkeys.[11] The occurrence of hemoglobinuria following intravenous injection of 50% urea solutions in animals has been the basis for considering solutions of this concentration as contraindicated clinically.[10]

Hemoglobinuria is never observed after 30% urea injection when 5% dextrose solution, rather than water, is used as the solvent.

Comment

The object of the present study was a limited one: to compare the hypotensive effect of four drugs. With this accomplished, and with results indicating that hypertonic urea is by far the most effective of the four agents, it becomes desirable to know more about the mechanism of urea action. Definitive answers must await application of more refined tonographic methods. At the present time these limited speculations appear justified.

Mechanism of Urea Action.—Settlage et al.[12] have presented evidence that the effects of urea on cerebrospinal fluid pressure are directly correlated with its diuretic action.

The period of lowest cerebrospinal fluid pressure corresponds with the period of maximum urine output. The effects of urea, therefore, appear to be due primarily to its marked diuretic effect. The present results are in good agreement with those obtained with the use of urea in the reduction of intracranial pressure. Similar mechanisms may be at work in both instances.

Recently de Roetth [7] studied the effects of changes in the osmotic presure of the blood on aqueous humor dynamics in man. Using tonographic measurements according to the method of Grant,[15] he found that osmotic changes in the blood affect the total rate of flow of aqueous in both normal and glaucomatous eyes. Hypertonic solutions cause a decrease in flow; hypotonic solutions, an increase. In glaucomatous eyes the facility of aqueous outflow is not appreciably changed by hypertonic sorbitol, while this monosaccharide sugar produced an appreciable alteration in facility of outflow in the normal eye. The response to sorbitol was reported to be of short duration. The maximum effect was seen at 30 minutes, with a return to normal in about 2 hours. In the present study the effects of the monosaccharide dextrose were found to be of even shorter duration (30 to 60 minutes).

The findings of Bellows and associates [16] are in conflict with the present results and with the observations of de Roetth. These workers observed the maximal reduction in intraocular pressure 12 to 24 hours after sorbitol injection. The diuretic effects of sorbitol in the dog begin within 15 to 30 minutes following intravenous injection.[17] It is completely cleared from the blood in about three hours.[18] Therefore, the protracted action described by Bellows et al. is difficult to accept. The absence of adequate control studies by Bellows et al. may account for this discrepancy.

It would seem reasonable to assume that hypertonic sorbitol and urea assert their actions through similar mechanisms. Increased urea in the blood (concentrations up to 90.0 mg/100 cc. have been observed after intravenous injection in the human [10]) results in an increased osmotic tension in the ciliary capillaries. This concentration alters the blood-aqueous osmotic relationships, with a resultant decrease in aqueous flow and a lowering of intraocular pressure. Secondarily, because of the obligatory water loss which occurs when urea is excreted, there is an increase in the colloidal concentration in the blood. Consequent upon this change in oncotic pressure of the blood plasma, there is a hypotensive effect on intraocular pressure during the full period of diuresis.

The absence of a secondary rise in intraocular pressure following hypertonic sugar or urea injections may be due to an active blood-aqueous barrier for these substances. As first pointed out by Adler [19] and Walker [20] in 1933, urea is present in lower concentrations (about 30%) in aqueous than in blood. Duke-Elder and Davson [21] found that nitrogenous substances penetrate the blood-aqueous barrier slowly (at about one-third the rate of the large-molecule sugars). Glucose is also present in the aqueous in diminished concentrations, owing to glucose utilization by the lens.[22] This lower concentration strongly suggests a blood-aqueous barrier, especially for nitrogenous substances, and may explain the absence of a secondary rise in intraocular pressure following glucose or urea injection.

Practical Considerations Related to the Use of Urea.—Urea is an old and established drug, recognized as an effective diuretic when taken in doses of 20 gm. two to five times a day. The necessity of using large doses to obtain the desired effect constitutes one of the disadvantages of urea, but it should be emphasized that the disadvantage is only mechanical. Effective doses are not large in the sense of approaching the limit of toxicity, in that they are expensive, or in that they put a strain on the organism.

The oral administration of urea presents an additional problem, for urea has an extremely disagreeable taste. Much of the difficulty of oral administration may be eliminated by using tablets. The tablets could be sugar-coated to eliminate the un-

pleasant taste completely. The taste problem is, of course, not present when the urea is given intravenously, by gastric tube, or subcutaneously. To the best of our knowledge, the latter route of administration has not been used clinically. A program of animal study is at present under way to determine the efficacy of subcutaneous administration.

In the earlier studies of the present series, difficulty was encountered in preparing sterile solutions of urea for intravenous use. The problem was solved with the help of Dr. Busse, of the University of Wisconsin Department of Pharmacy. The fact that sterile urea preparations are not commercially available presents a problem for potential urea users wishing to employ the parenteral route. In actuality, sterile solutions are easily prepared.*

There has been earlier mention in this report of the problem of hemoglobinuria and the means of avoiding hemolysis of the red blood cells. The matter of toxic effects, and what are considered important precautions, has been considered at length in another publication.[10]

Turning from the consideration of problems and disadvantages, we may point out some advantages of urea. Urea is highly effective, in comparison with hypertonic sugars and acetazoleamide, for the reduction of intraocular pressure in normal monkeys. The finding that urea was remarkably effective for the reduction of cerebrospinal fluid pressure in the monkey led to the trial of this agent in man. The results met all expectations. This consideration would seem to justify investigation of the efficacy of urea for the control of elevated intraocular pressures in man. One might expect that elevated intraocular pressures would respond more dramatically to urea than do normal pressures. This has been found to be the case with elevated cerebrospinal fluid pressure.[10]

Secondly, no toxic effects have been observed following large doses, and none are expected if reasonable precautions are observed. Urea is a normal body metabolite; it has been designated by Salter[23] as "nature's own non-electrolytic diuretic." Both oral and parenteral routes are available for administration. Rectal administration has not proved feasible, because of prompt and vigorous expulsion. Finally, it has been observed in cerebrospinal fluid pressure studies that urea continues to be effective in lowering pressures after doses have been given several times daily over a period of weeks.[12] The final evaluation of the role of urea in the treatment of conditions of increased intraocular pressure must await repeated trials in the ophthalmology clinic.

Summary and Conclusions

Intravenous injections of 5 cc/kg. of 50% dextrose, 5 cc/kg. of 50% sucrose, 2.5 cc/kg. of 30% urea, 5.0 cc/kg. of 30% urea, 5.0 cc/kg. of 50% urea, and 50 mg/kg. of acetazoleamide (Diamox) were performed in seven monkeys in 22 experimental sessions to determine the effects on the normal intraocular pressure. The injections were preceded by a 2-hour control period; the intraocular pressure was followed for 10 hours thereafter.

The normal intraocular pressure in the monkey was found to be approximately 26 scale units of the McLean tonometer. Anesthesia alone generally resulted in a gradual fall during the 12-hour observation period.

Urea, 5.0 cc/kg. of 30% solution, produced more pronounced and more prolonged pressure drops than did dextrose, sucrose, or acetazoleamide. The duration of the effect averaged three hours. The magnitude of pressure reduction was more than 15 scale units of the McLean tonometer.

Toxic effects were noted only in the case of administration of 5 cc/kg. of 50%

* Dr. Louis Busse, Department of Pharmacy, University of Wisconsin, has expressed his willingness to provide the necessary advice and assistance for the preparation of sterile urea by local pharmacies. Inquiries may be directed to Dr. Busse by pharmacists who would be responsible for preparation of sterile solutions or by the interested physicians themselves.

urea, which produced a transient hemoglobinuria. The more dilute urea solutions produced no toxic effects.

It is suggested that urea may be useful in the management of increased intraocular pressure in man.

Department of Anatomy, Science Hall, University of Wisconsin (6).

REFERENCES

1. Duke-Elder, W. S.: The Reaction of the Intra-Ocular Pressure to Osmotic Variations in the Blood, Brit. J. Ophth. 10:1-19 (Jan.) 1926.

2. Benham, G. H.; Duke-Elder, W. S., and Hodgson, T. H.: Osmotic Pressure of the Aqueous Humor in the Normal and Glaucomatous Eye, J. Physiol. 92:355-360 (April) 1938.

3. Duke-Elder, W. S., and Davson, H.: The Present Position of the Problem of the Intraocular Fluid and Pressure, Brit. J. Ophth. 32:555-569 (Sept.) 1948.

4. Kinsey, V. E.: Chemical Composition and Osmotic Pressure of Aqueous Humor and Plasma of Rabbit, J. Gen. Physiol. 34:389-402 (Jan.) 1951.

5. Friedenwald, J. S.: Dynamic Factors in Formation and Re-Absorption of Aqueous Humor, Brit. J. Ophth. 28:503-510 (Oct.) 1944.

6. Kinsey, V. E.: A Unified Concept of Aqueous Humor Dynamics and the Maintenance of Intraocular Pressure: Elaboration of the Secretion-Diffusion Theory, Arch. Ophth. 44:215-235 (Aug.) 1950.

7. de Roetth, A., Jr.: Effect of Changes in Osmotic Pressure of Blood on Aqueous Humor Dynamics, A. M. A. Arch. Ophth. 52:571-582 (Oct.) 1954.

8. Hertel, E.: Experimentelle Untersuchungen über die Abhängigkeit des Augendrucks von der Blutbeschaffenheit, von Graefes Arch. Ophth. 88: 197-229 (June) 1914.

9. Fremont-Smith, F., and Forbes, H. S.: Intraocular and Intracranial Pressure: An Experimental Study, Arch. Neurol. & Psychiat. 18: 550-564 (Oct.) 1927.

10. Javid, M., and Settlage, P.: Effect of Urea on Cerebrospinal Fluid Pressure in Human Subjects: Preliminary Report, J. A. M. A. 160:943-949 (March 17) 1956.

11. Smythe, L.; Smythe, G., and Settlage, P.: The Effect of Intravenous Urea on Cerebrospinal Fluid Pressure in Monkeys, J. Neuropath. & Exper. Neurol. 9:438-442 (Oct.) 1950.

12. Javid, M.; Settlage, P. H., and Monfore, T.: Urea in the Management of Increased Intracranial Pressure, S. Forum, to be published.

13. Settlage, P. H.; Javid, M., and Monfore, T.: Urea for the Control of Intracranial Pressure, to be published.

14. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1955.

15. Grant, W. M.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. 44:204-214 (Aug.) 1950.

16. Bellows, J.; Puntenney, I., and Cowen, J.: Use of Sorbitol in Glaucoma, Arch. Ophth. 20: 1036-1043 (Dec.) 1938.

17. West, E. S., and Burget, G. E.: Sorbitol as a Diuretic, Proc. Soc. Exper. Biol. & Med. 35: 105-107 (Oct.) 1936.

18. Rosner, L., and Bellows, J.: The Passage of Sorbitol from the Blood into the Aqueous Humor and the Cerebro-Spinal Fluid, Am. J. Physiol. 125:652-657 (March) 1939.

19. Adler, F. H.: An Investigation of the Sugar Content of the Ocular Fluids Under Normal and Abnormal Conditions, and the Glycolytic Activity of the Tissues of the Eye, Tr. Am. Ophth. Soc. 28:307-340, 1930.

20. Walker, A. M.: Comparison of Chemical Composition of Aqueous Humor, Cerebrospinal Fluid, Lymph, and Blood from Frogs, Higher Animals, and Man: Reducing Substances, Inorganic Phosphate, Uric Acid, Urea, J. Biol. Chem. 101:269-287 (June) 1933.

21. Duke-Elder, W. S., and Davson, H.: The Significance of the Distribution Ratios of Non-Electrolytes Between Plasma and the Intra-Ocular Fluid, Brit. J. Ophth. 27:431-434 (Oct.) 1943.

22. Sugar, S. H.: The Glaucomas, St. Louis, The C. V. Mosby Company, 1951.

23. Salter, W. T.: A Textbook of Pharmacology: Principles and Application of Pharmacology to the Practice of Medicine, Philadelphia, W. B. Saunders Company, 1952.

The Radioactive Phosphorus Uptake Test for Malignant Melanoma of the Eye

A Study of Forty Consecutive Cases of Suspected Intraocular Malignant Melanomas

ANTHONY DONN, M.D., and JOHN W. McTIGUE, M.D., New York

Introduction

Since the first report by Thomas, Krohmer, and Storaasli, in 1952,[1] many excellent studies have confirmed the fact that the measureable uptake of radioactive phosphorus is greater over malignant melanomas of the eye than over normal ocular tissue, intraocular hemorrhage, or serous retinal detachments.[2-14] A wealth of case reports in these papers documents the fact that this difference in uptake may be used clinically to distinguish a malignant melanoma from a more benign condition in the eye. As the experience with this technique has increased, however, it has also become apparent that there are three important limitations to the clinical effectiveness of this test: (1) Lesions at the posterior pole may not be accessible to the probe counter; (2) inflammatory lesions may give false-positive readings for malignant melanomas; (3) inaccuracies inherent in the counting procedure may give false results. For these reasons, a good deal of skepticism remains among many ophthalmologists as to the empirical value of the test in actual practice. In an attempt to evaluate further the clinical usefulness and limitations of this procedure, the present work was undertaken. The reliability of this test was appraised in 40 consecutive cases of suspected intraocular malignant melanomas.

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Methods

In all cases the radioactive-phosphorus-uptake test was performed according to the procedure detailed by Terner, Eisenberg, and Leopold.[8,13] The dose of P^{32} was approximately 500μ for a normal adult.* Readings were taken with a straight Anton probe counter over the control eye and over the suspected eye 1 hour and 24 hours after the administration of the phosphorus isotope. A minor modification of technique was employed in obtaining control counts. Instead of using the average of readings taken at the limbus of the normal eye, control readings were made at only one spot on the normal eye, at a location which corresponded to the site of the lesions in the suspected eye. The criteria which we employed to indicate the presence of a malignant lesion are those which were described by Eisenberg, Terner, and Leopold: At 1 hour the ratio of the measureable radioactivity over the lesion compared with the control eye must be at least 1.3:1, and at 24 hours this ratio must be greater than the one-hour ratio.

This ratio of 1.3:1 is an arbitrary boundary which has been derived empirically by

* Although the amount of total body radiation from this dose is roughly seven times greater than the maximum permissible dose established by the National Committee on Radiation Damage, its use is approved by this committee on the same grounds that a gastrointestinal x-ray series (which also provides much more than the maximum permissible dose) is justified—where possible diagnostic benefit to the patient outweighs the risk of the radiation. In the case of pregnant women, however, this dose of P^{32} is contraindicated, as embryonic tissue is much more sensitive to radiation than normal adult tissue.

other workers. For this reason, it is important to understand the large errors which are inherent in the testing procedure and to evaluate the reliability of a given result. In our experience the variation between any two sucessive counts over the same spot in a normal eye may run as high as ±12%. Thus, if one took only one reading at each of two spots a ratio of 1.25:1 might occur simply from the range of error in the counting procedure. There are two main sources of error. One of these stems from the random nature of the decay of a radioactive isotope. Even if all other conditions of the testing procedure could be rigidly controlled, the random disintegration of the radioactive isotope as employed in this test could account for a variation of about ±7% in consecutive readings.† Superimposed on this source of error is the error introduced by slight changes in position of the probe counter during successive one-minute counting periods. It is not possible to quantitate this error, for under some conditions a small change in position will make no appreciable difference, whereas when counting over a small malignant lesion a change of position of 1 to 2 mm. may remove a large part of the lesion from the face of the probe counter. Both of these sources of error can be greatly reduced by increasing the number of one-minute readings at each spot and using the average result. This decreases the error from the random disintegration of the isotope and decreases the variation due to small changes in the position of the probe. The reliability of the resulting ratios are thus increased. In this series we counted a minimum of five separate one-minute intervals at each spot and used the average of these readings. In any case, where the ratios were close to the arbitrary figure of 1.3:1 we would take five more separate one-minute counts at each spot and average these values with the earlier ones.

$$\frac{100}{\sqrt{230}}=7\%.$$

†The usual one-minute reading in a normal adult one hour after 500μc of P^{32} is of the order of magnitude of 230 counts;

Selection of Cases

This study was limited to only those consecutive cases in which the possibility of malignant melanoma was considered on clinical grounds. All of the patients who were studied were referred by qualified ophthalmologists because some question arose in the eye examination as to the possibility of a malignant lesion in the eye. These patients fell into three categories.

The first group is comprised of 34 patients who presented a discrete, ophthalmoscopically visible, lesion in the fundus. (In one patient the lesion was on the iris.) These patients had in common only the suspicion on the part of the ophthalmologist that a malignant melanoma might be responsible for the ophthalmoscopic lesion. Naturally, the lesions varied greatly, as did the index of suspicion of the ophthalmologist. For example, in some cases a malignant melanoma was strongly suspected but confirmation was requested because there were disturbing features, such as an accompanying hole in the retina or smallness of the lesion or youth of the patient (23 years), or a difference in opinion among consultants. At the other pole were cases in which malignant melanoma was thought unlikely but, nevertheless, a possibility to be ruled out. In this group were serous detachments in which no hole could be found or in which transillumination was equivocal or in which the intraocular pressure was elevated.

Group 2 consists of three patients, each of whom had a blind eye with opaque media. It was requested that a screening be performed over the entire eye with the probe counter to rule out the presence of a gross malignant melanoma.

The third group is composed of three patients who had had a discrete elevation of the retina treated with diathermy and who were suspected, after surgery, of having a melanoma because of such features as a rise in tension or progression of the elevation.

Results and Comment

Of the 34 cases in Group 1, the test was positive for malignant melanoma in 17, ac-

cording to the criteria described above. All 17 eyes were enucleated, and all proved by histological examination to contain malignant melanomas. Thus, in this series there were no false-positive results. In the literature there have been occasional reports of false-positive results, usually associated with inflammatory lesions. We do not doubt that these may occur, but in our series, where cases were selected only by the clinical suspicion of melanoma, no false-positive results occurred. It is probable that cases with frank inflammatory signs were recognized as such clinically and not referred for the P^{32}-uptake test.

The remaining 17 cases of Group 1 gave negative results. Of these negative cases, five presented lesions which were patently too far posterior to be reached by the probe counter. It was realized at the time of testing that these lesions were probably not accessible. In such cases, however, testing is still carried out, because, although negative results have no significance (neither ruling out nor detecting a malignant lesion), positive results still provide legitimate confirmation of a melanoma. Of these five cases, four eyes were enucleated on the basis of clinical findings and one case is being followed. Three of the four enucleated eyes proved to have a melanoma, while the fourth case was discovered to be a hemangioma of the choroid. Thus, of 34 consecutive discrete lesions suspected of being malignant melanoma, 5 were too far posterior for the radioactive phosphorus test to be of any value. It is important that many lesions, especially those temporal to the macula, are more accessible than they might seem at first. Even in those cases when it is uncertain whether the lesion can be reached, a positive result provides definite confirmation and the test is worth attempting.

The remaining 12 negative results in Group 1 were obtained over readily accessible sites. There is one documented false-negative result in this group. This occurred in an iris lesion; the eye was enucleated on clinical grounds, and the iris contained a flat malignant melanoma. There was no striking histological pattern to explain the failure of the tissue to retain more of the injected phosphorus.‡ The other 11 negative cases have been followed for periods from 4 to 14 months, and no new clinical evidence of malignancy has been noted.

The three cases in Group 2 had negative results, and no new evidence of malignancy has appeared in the follow-up period of eight months to one year. This type of screening procedure, however, is unsatisfactory, and we have discontinued its use. This screening of an opaque eye could be of value if a positive result was obtained, but, in our opinion, a negative result is worse than meaningless, because it may give a false sense of security. Despite careful counting over the entire exposure sclera, one cannot be certain that a small lesion or a posterior lesion is not present.

All three of the eyes in Group 3, which had received diathermy from one month to five months prior to testing, showed ratios greater than 1.3:1 at the end of one hour. In addition, two of these cases showed no fall in this ratio at 24 hours, while the third case exhibited a small decrease in the ratio. In one of these cases which showed no fall in the 24-hour ratio, the eye was enucleated on clinical grounds and proved to have no malignancy. The two other cases have been followed for nine months, and no new evidence of melanoma has presented.

Terner [13] has reported similar results in patients treated for detachments. Thus, even on the basis of a few cases, the evidence seems clear that a positive result has no significance in the presence of previous diathermy treatment, even when the diathermy was given months before the P^{32} test. It is significant in this connection that some workers [8,13] believe that an inflammatory lesion can be distinguished from a neoplastic one by the change of the 24-hour ratio as compared with the 1-hour ratio.

‡ Since the measureable uptake of phosphorus, however, is in part a function of the mass of tissue in front of the probe, it is probable that the very flat nature of the lesion accounts, mechanically, for the absence of a positive result.

In this series we have not tested idiopathic inflammatory lesions, but it would seem that diathermy treatment sets up a controlled inflammation, and, in our limited experience with these eyes, the above criteria fail to distinguish inflammatory from malignant lesions.

Summary

The reliability of the P^{32}-uptake test was studied in 40 consecutive cases of suspected malignant melanoma of the eye. In this series the results were as follows:

(*a*) There were no false-positive uptake tests of 34 eyes suspected of having malignant melanomas. Seventeen showed positive uptakes. In all 17 the eye was enucleated, and all contained the lesion.

(*b*) There was one documented false-negative test. This occurred in an iris lesion which proved to be a malignant melanoma on enucleation.

(*c*) Five cases had lesions which were inaccessible to the probe counter and gave negative uptake tests which were meaningless.

(*d*) Positive tests are not reliable in the presence of previous diathermy treatment.

In our experience, the greatest clinical value of the radioactive-phosphorus-uptake test is in providing objective confirmation of suspected malignant melanomas.

Dr. Ludwig von Sallmann assisted in beginning this study, and the Attending Physicians of the Institute of Ophthalmology referred these cases to us.

622 W. 168th St. (32).

REFERENCES

1. Thomas, C. I.; Krohmer, J. S., and Storaasli, J. P.: Detection of Intraocular Tumors with Radioactive Phosphorus: A Preliminary Report with Special Reference to Differentiation of the Cause of Retinal Separation, A. M. A. Arch. Ophth. 47:276, 1952.

2. Town, A. E.: Radioactive Phosphorus Studies in the Diagnosis of Ocular Tumors: A Preliminary Report, West Virginia M. J. 48:356, 1952.

3. Dunphy, E. B., and Selverstone, B.: Uptake of Radioactive Phosphorus by Normal and Neoplastic Ocular Tissues, Am. J. Ophth. 36:774, 1953.

4. Town, A. E.: Radioactive Phosphorus Studies in the Diagnosis Between Solid and Serous Detachment of the Retina, Pennsylvania M. J. 56: 1046, 1953.

5. Dunphy, E. B.; Dreisler, K. K.; Cadigan, J. B., and Sweet, W.: The Uptake of Radioactive Phosphorus by Intraocular Neoplasms, Am. J. Ophth. 37:45, 1954.

6. Thomas, C. I.; Krohmer, J. S.; Storaasli, J. P., and Friedhill, H. L.: Detection of Intraocular Tumors by the Use of Radioactive Phosphorus, Am. J. Ophth. 38:93, 1954.

7. Eisenberg, I. J.; Leopold, I. H., and Sklaroff, D.: Use of Radioactive Phosphorus in Detection of Intraocular Neoplasms, A. M. A. Arch. Ophth. 51:633, 1954.

8. Eisenberg, I. J.; Terner, I. S., and Leopold, I. H.: Use of P^{32} as an Aid in Diagnosis of Intraocular Neoplasms: Further Observations, A. M. A. Arch. Ophth. 52:741, 1954.

9. Kennedy, R. J.; Glasser, O., and Kazdan, P.: The Use of Radioactive Phosphorus in the Detection of Intraocular Tumors, Cleveland Clin. Quart. 21:133, 1954.

10. Bettman, J. W., and Fellows, V.: Radioactive Phosphorus as a Diagnostic Aid in Ophthalmology, A. M. A. Arch. Ophth. 51:171, 1954.

11. Thomas, C. I.; Krohmer, J. S., and Storaasli, J. P.: Geiger Counter Probe for Diagnosis and Localization of Posterior Intraocular Tumors, A. M. A. Arch. Ophth. 52:413, 1954.

12. Palin, A., and Tudway, R. C.: The Use of Radioactive Isotopes in the Diagnosis of Intraocular Malignancy, Tr. Ophth. Soc. U. Kingdom 75:281, 1955.

13. Terner, I. S.; Leopold, I. H., and Eisenberg, I. J.: The Radioactive Phosphorus (P^{32}) Uptake Test in Ophthalmology: A Review of the Literature and Analysis of Results in 262 Cases of Ocular and Adnexal Pathology, A. M. A. Arch. Ophth. 55:52, 1956.

14. Owens, W. C.; King, J. H., Jr., and Weils, H. S.: Radioactive Phosphorus for the Detection of Intraocular Tumors. Am. J. Ophth. 41:507, 1956.

On the Existence of an Embryonic Lens Protein

JULES FRANCOIS, M.D., and MARCEL RABAEY, M.D., Ghent, Belgium

Since the investigations of Mörner,[12] Krause,[11] and Schaeffer and Murray[13] it has generally been accepted that in the eye lens of the cow there exist three water-soluble proteins, the α-β, and γ-crystallins. The last one is found in very small concentration, less than 2% of the total protein (Table 1) and can be considered a residual protein, remaining in solution after maximal precipitation of the α-and β-crystallins.

Even if the γ-crystallin is really a distinct protein, it would hardly be disclosed by electrophoresis, as it only amounts to less than 2%, and we could omit it in this work from our considerations.

As we have already shown previously (1953), paper electrophoresis reveals in the bovine lens three protein fractions existing in high concentrations: 1. Fraction I, the most rapidly moving component, corresponds to α-crystallin, the purity of which we have ascertained in an investigation as yet unpublished. 2. Fraction II, which shows the highest concentration, is certainly not homogeneous (1954). 3. A third protein also exists, in a relatively high concentration; this is Fraction III and is the slowest component, which remains in the vicinity of the starting point when a buffer solution of pH 8.6 is employed.

By numerous electrophoretic investigations we have been able to establish the following facts: 1. In the cow and in numerous other mammals which we have examined, Fraction III shows the highest concentration in the nuclear part of the lens, where, in contrast, is the α-crystallin proportionally diminished. 2. In the cow Fraction III is almost totally absent in the more external layers of the cortex. 3. The percentage of Fraction III increases gradually from the outer towards the central layers of the lens.

Croisy already had suspected in 1952 the existence of a third protein fraction. "The first coloured band partly overlaps the deposition spot on the filter paper and shows maximum colouration at a point slightly behind of the line of departure." He was, however, cautious in his conclusions: "Whilst the existence of constituents 2 and 3 can be ascertained with certainty, we have to make reservations as to constituent 1 [constituents 3, 2, and 1 from Croisy are, respectively, Fractions I, II, and III]. In fact, this is represented in the electrogram by a coloured band which is superimposed on the point of deposition of the protein solution as a result of which its interpretation should be cautious. The comparison of the electro-chromatograms obtained, with equilibrated levels of the containers and with the level of cathode raised, contributes a

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From the Ophthalmological Clinic of the University of Ghent; Director: Prof. J. François. Qualified Research Worker of the "Fonds National de la Recherche Scientifique" (Dr. Rabaey).

TABLE 1.—*Proportions of Protein Fractions in the Bovine Lens*

	Protein Fraction, %			
	Albuminoid	α-Crystallin	β-Crystallin	γ-Crystallin (Albumin)
Mörner	48.6	19.4	31.4	0.6
Krause	12.50	31.74	53.30	1.46
Schaeffer	11.9	31.1	51.5	1.4

fact which supports the existence of this constituent: the raising of the cathode vessel has as a result the determination of a weak displacement of this first coloured band towards the anode; this displacement is less important than that of the second and third coloured band but is all the same very clear."

Recently Bon [1] could not accept the existence of a third protein fraction. He considers it simply as a product of denaturation of the ageing α-crystallin. It is true that the special behavior of Fraction III can be adduced in favour of the above opinion. In the discussion of Stemmermann's communication we already noted some of the special characteristics of this protein. For instance, its adsorption on filter paper is so strong that one can by this means separate it by a sort of chromatography.

Two hypotheses can be put forward, then, regarding the nature of Fraction III: (*a*) It is a denaturation product of α-crystallin and appears, especially in the nucleus of the lens, in the course of the latter's ageing or (*b*) it is a distinct protein, formed only in early stages of the development of the lens.

With a view to testing these hypotheses, we examined 30 lenses, not only from calfs and cattle of 0 to 10 years old but also from embryos of varying lengths; the smallest embryo examined was 3.5 cm. long.

We have classified the lenses according to the total amount of proteins as determined by micro-Kjeldal analysis, in most cases, and, in some cases, by Biuret's colorimetric method. The total water-soluble extract of the lens, consisting of the three fractions in nearly equal concentration, contained 16.92 gm. of nitrogen per 100 gm. of dry protein.

Our results are given in Table 2, where the total protein weights in milligrams and the percentage of the various fractions are given. Each figure represents the mean from five different electrophoreses, carried out by the qualitative and quantitative method we have previously described (1953). The absolute quantities in milligrams of N for the three fractions of each lens are also given. It should be recalled in this connection that neither nitrogen dosage nor any other method measures exactly the concentration of a protein solution. The N content of the three protein fractions

TABLE 2.—*Protein Fractions and Nitrogen in Cattle Lens*

Age and Length	Total Protein in Lens, Mg.	Percentage of Fractions			N in Fractions, Mg.		
		I	II	III	I	II	III
Embryo							
GE 3.5 cm. (Fig.1)		42.2	39.1	18.7			
MI 6.7 cm.	1.49	33.6	42.85	23.55	0.0805	0.101	0.056
NN 7 cm.	3.22	32.35	43.7	23.95	0.175	0.232	0.127
RN 7 cm.		35.0	41.9	23.1			
SU 8.7 cm. (Fig. 2)	4.39	30.7	37.25	32.05	0.221	0.269	0.231
CH 12 cm.	9.80	28.3	40.9	30.8	0.455	0.658	0.495
FR 3 mo.	13.95	30.5	38.6	30.9	0.698	0.884	0.708
BR 3¼ mo. (Fig. 3)	22.49	30.3	38.1	31.6	1.08	1.36	1.13
BT	23.46	29.5	38.6	31.9	1.14	1.49	1.23
MAN 3½ mo.	28.3	28.75	38.25	33.0	1.337	1.778	1.534
DA 3½ mo.	37.23	30.05	36.6	33.35	1.84	2.24	2.04
DI 3½ mo.	46.80	29.1	37.8	33.1	2.29	2.90	2.54
MAR 4 mo.	68.85	30.0	38.78	31.22	3.44	4.44	3.57
HE 4 mo.	95.74	29.6	37.75	32.65	4.65	5.93	5.13
BER 5½ mo. (Fig. 4)	101.06	28.8	36.2	35.0	4.76	5.98	5.77
KA 6 mo.	130.61	30.2	37.7	32.1	6.50	8.12	6.93
GU 6 mo. (Fig. 5)	147.8	31.4	37.1	31.4	7.67	9.06	7.67
JU 6 mo.		30.2	39.8	30.1			
PI 7 mo.	180.3	30.0	39.4	30.6	8.80	11.67	9.05
RU 8 mo. (Fig. 6)	184.4	31.5	39.75	28.75	9.68	12.20	8.82
RO 8½ mo.	240.54	31.3	39.75	28.95	12.54	15.94	11.61
Animal							
AD 3 mo. (Fig. 7)	359.3	33.95	42.5	23.55	19.9	24.9	13.8
JN 6 mo. (Fig. 8)	521.9	34.4	43.9	21.6	29.6	37.6	18.2
MAC 1 yr.	639.5	35.7	47.1	17.2	37.1	49.0	17.9
FR 2 yr.	680.8	35.5	49.0	15.5	40.4	55.75	17.65
AN 3 yr.	768.3	34.8	47.3	17.9	41.8	56.8	21.5
BD 4 yr. (Fig. 9)	874.7	33.0	50.6	16.4	42.34	64.92	21.04
ST 7 yr.	927.9	33.7	54.1	12.2	40.8	65.5	14.7
BES 8 yr. (Fig 10)	887.7	35.4	57.4	15.1	35.6	58.0	15.4
JA 10 yr.	874.7	29.2	54.75	16.05	34.5	64.7	19.0
PO 10 yr.	981.1	30.6	54.9	14.5	38.8	69.6	19.4

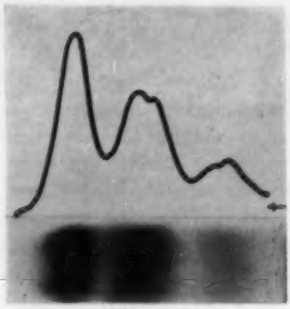


Figure 1

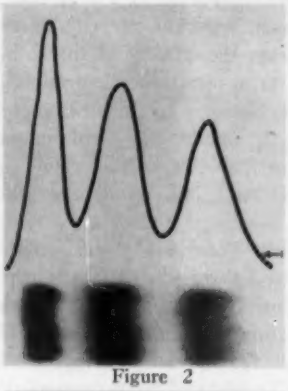
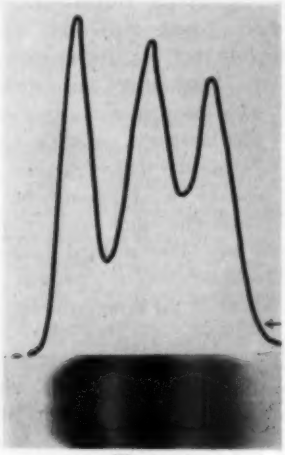


Figure 2



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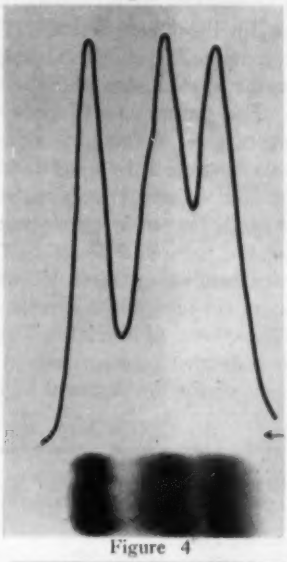
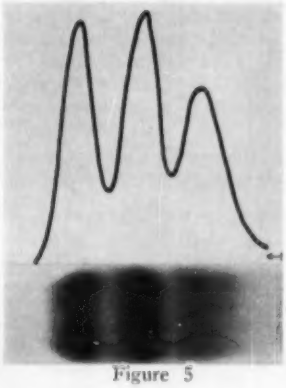


Figure 4



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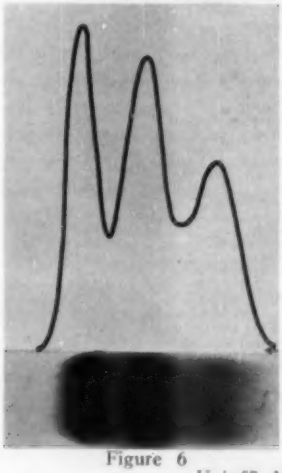

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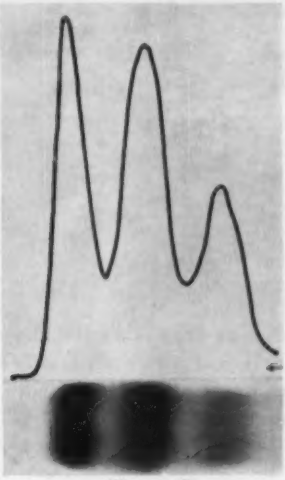

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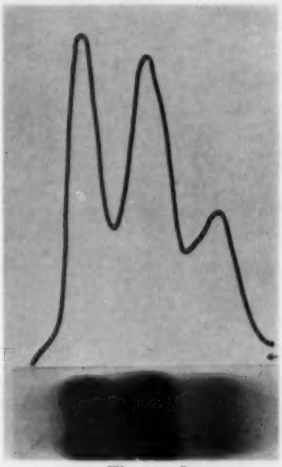

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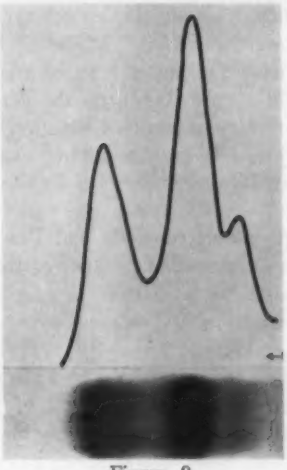

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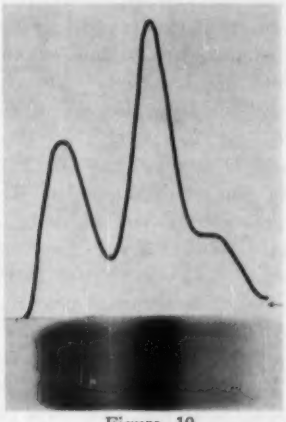


Figure 10

of the lens is not yet known with certainty; it is certain, however, that it differs only very little. The method is, all the same, valid, since our aim was to allow the three large protein fractions in relation to the increase of lens weight, or rather to total protein synthesis, i.e., to lens growth.

We have also examined separately the cortical part of the nuclear region of a dozen lenses (Tables 3 and 4). As the separation of cortex and nucleus is very arbitrary, especially in the embryo, we give the wet weights of the examined parts in relation to the total wet weight of the lens.

For each lens we have also determined the percentage of water-soluble proteins and of albuminoid (insoluble). These are given in Table 5.

Comment

Our various investigations establish the following facts: 1. During embryonic life Fraction III appears at a very high concentration, namely, 18% to 24% of water-soluble protein in bovine embryos of a length less than 7 cm. and more than 30%

TABLE 3.—*Comparison of Weights of Cortical Region and Total Lens*

Age	Wet Weight of Cortical Region, Mg.	Wet Weight of Total Lens, Mg.	Percentage of Fractions		
			I	II	III
Embryo					
BR 3¼ mo. (Fig. 11)	46.49	105.75	31.4	38.1	30.2
DA 3½ mo.	122.5	158.6	21.85	41.0	27.15
MAR 4½ mo.	192.3	278.02	31.8	38.9	29.5
KA 6 mo.	227.1	552.2	32.2	42.2	25.6
JU 6 mo.	270.0	408	33.5	40.3	26.1
Animal					
AD 3 mo. (Fig. 12)	579.3	1.169.6	37.5	49.5	13.0
AN 3 yr.	676.5	2.164.6	44.1	52.8	3.1
BD 4 yr. (Fig. 13)	741.7	2.466	45.5	52.0	2.5
JA 10 yr.	826.4	2.619.8	43.1	56.9	..

in embryos longer than 7 cm. 2. At least in embryos larger than 7 cm., during the embryonic period up to birth, the concentration of the various fractions remains remarkably constant: The three protein fractions increase simultaneously in a linear fashion (Fig. 17). 3. After birth the situation changes. While Fractions I and II continue to increase progressively, the concentration of Fraction III diminishes significantly so that the absolute quantity of it in the lens increases very little after birth and not at all after the age of 6 months (Fig. 18).

It could be argued that this lack of increase of the soluble Fraction III is due to precipitation of part of it as insoluble albuminoid. In embryos the amount of albuminoid is very small (3% to 5%), but it remains small also for some time after birth. At the age of 1 year soluble protein accounts for 96%; at 3 years, for 92%, and at 4 years, for 87% of the lens total. From that point on, the percentage of albuminoid rises markedly. But also from that point on it can be seen (Fig. 18) that Fraction I (α-crystallin) diminishes while Fraction II increases linearly and Fraction III remains practically unchanged. These facts allow the conclusion that the percentage of albuminoid rises to a large extent by the precipitation of the α-crystallin in the nuclear part of the lens.

4. These facts are further substantiated by comparing the cortical and the nuclear part of the lens. During embryonic life the two parts differ only slightly in the percentages of their various protein fractions. After birth, however, only a minute quantity of Fraction III is synthesised in the cortical region.

We may thus conclude that Fraction III is not a denaturation product of the ageing α-crystallin but a distinct protein which is synthesized, in the bovine lens at least, during embryonic life only.

At birth the lens of the calf already contains two-thirds of the amount of Fraction III found at 10 years of age, while in this period the total quantity of proteins increases fourfold. The lens of a 6-month-old calf contains as much embryonic protein

TABLE 4.—*Comparison of Weights of Nuclear Region and Total Lens*

Age and Length	Wet Weight of Nuclear Region, Mg.	Wet Weight of Total Lens, Mg.	Percentage of Fractions		
			I	II	III
Embryo					
RN 7 cm.	..	..	28.6	41.1	30.3
BR 3¼ mo. (Fig. 14)	17.85	105.75	26.35	36.75	36.9
DA 3½ mo.	61.6	158.6	28.3	35.9	35.8
MAR 4½ mo.	59.0	278.02	28.3	34.8	36.9
KA 6 mo.	245.8	552.2	27.9	35.7	36.4
JU 6 mo.	231.5	408	28.6	36.2	35.2
Animal					
AD 3 mo. (Fig. 15)	330.7	1.169.6	31.6	36.4	32.0
AN 3 yr.	770.5	2.164.6	32.8	39.6	27.4
BD 4 yr. (Fig. 16)	911.3	2.466	23.6	49.5	26.9
JA 10 yr.	893.8	2.619.8	10.4	44.1	45.4

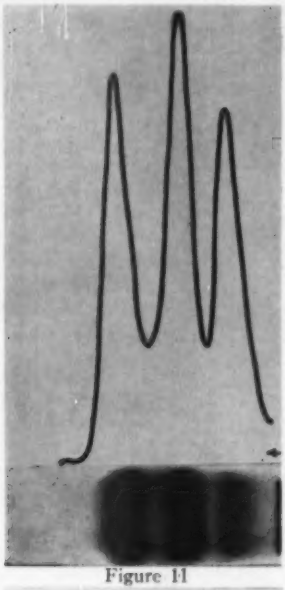
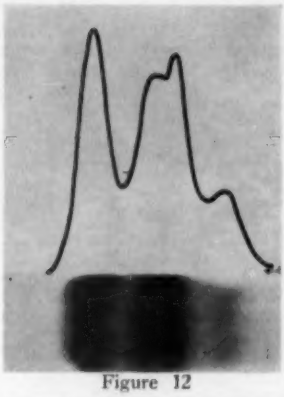


Figure 11



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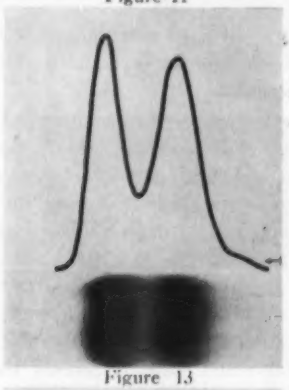

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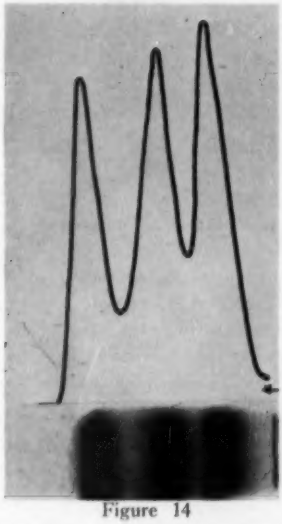

Figure 14

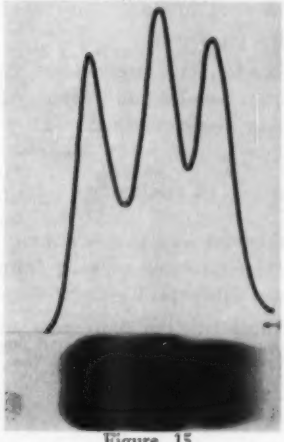

Figure 15

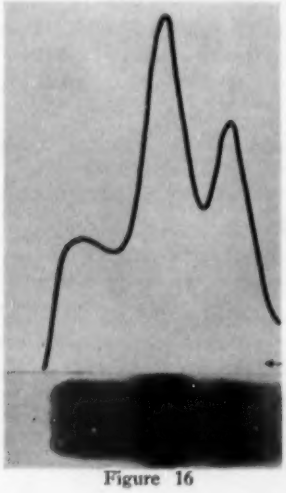

Figure 16

TABLE 5.—*Percentage of Water-Soluble Proteins in Lens*

	Net Weight of Lens, Mg.	Total Protein N, Mg.	Water-Soluble Protein N, Mg.	Soluble Protein, %
CE	--	--	--	--
MI	9.95	0.2515	(0.239)	(97)
NN	16.85	0.545	(0.53)	(97.5)
RN	--	--	--	--
SU	23.2	0.743	(0.721)	(97)
CH	66.28	1.658	(1.658)	(97)
FR	69.95	2.63	2.29	97
BR	105.75	3.805	3.57	94
BT	134.78	3.97	3.85	97
MAN	138.22	4.79	(4.65)	(97)
DA	158.6	6.30	6.12	97.5
DI	213.76	7.92	7.68	97
MAR	278.02	11.55	11.45	98
HE	343.47	(16.2)	15.7	(97)
BER	385.25	17.1	16.5	97
KA	552.2	22.2	21.55	97.5
GU	548.6	25.0	24.4	98
JU	--	--	--	--
PI	536.65	(30.5)	29.6	(97)
RU	666.2	31.2	30.7	98
RO	798.8	40.7	40.1	98
AD	1,169	60.8	58.7	97
JN	1,530	88.3	84.3	95
MAC	1,934	108.7	104.0	96
FR	2,053	115.2	113.8	98
AN	2,165	130.0	120.0	92
BD	2,466	148.0	128.3	87
ST	2,644	157.0	121.0	75
BER	2,532	150.2	109.0	67
JA	2,620	148.2	118.2	80
PO	2,755	166.0	126.8	75

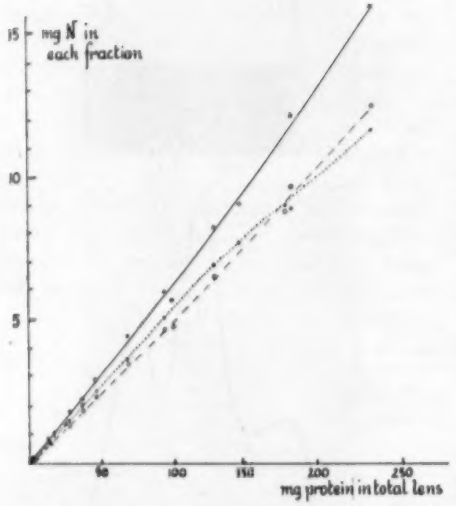

Fig. 17.—Increase of the three protein fractions of the bovine lens in function of the total protein synthesis during the embryonic period. Dashed line, Fraction I (α-crystallin). Solid line, Fraction II. Dotted line, Fraction III.

as the lens of a 10-year-old, while the total amount of protein is doubled during the same period.

A further proof that we are dealing with a distinct embryonic protein is provided by electrophoresis in agar, by which already in 1955 we succeeded in isolating Fraction III of the nucleus, during a study of its mobility at different pH values. This method shows up three large protein fractions, as illustrated in the case of the embryonic lens of a Calf BER, aged 5½ months, and as shown also in Figure 19. Under these conditions there is no question of separation by adsorption on paper.

Finally, we have found this embryonic protein in the human, too, as we shall describe in another paper.

Conclusions

In the bovine lens there exists a third important water-soluble protein fraction distinct from other proteins.

This third fraction represents an embryonic protein, the discovery of which should be credited to paper electrophoresis.

2, Avenue Pasteur.

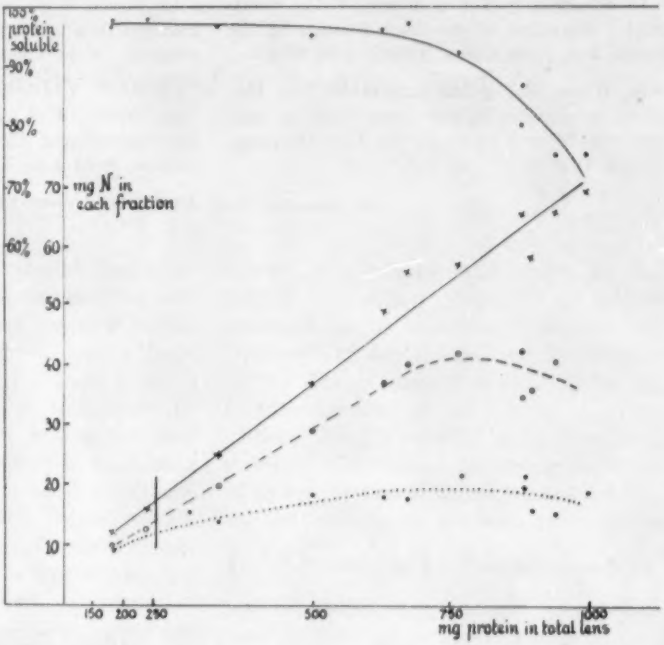

Fig. 18.—Increase of the three protein fractions of the bovine lens in function of the total protein synthesis after birth (marked by vertical line). Dashed line, Fraction I (α-crystallin). Solid line, Fraction II. Dotted line, Fraction III. At the top of the Figure is shown the curve of percentage of the soluble proteins.

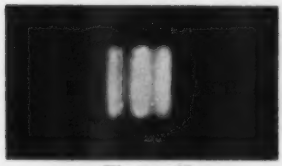

Figure 19

REFERENCES

1. Bon, W. F.: Physisch-chemisch onderzoek van het ooglenseiwit alpha-crystalline, thesis, Amsterdam, 1955.

2. Croisy, A.: Étude comparée des protéines cristalliniennes de l'homme (cristallins normaux et cataractés) et de divers animaux par l'électrophorèse sur papier, thesis, Marseilles, 1952.

3. François, J.; Wieme, R. J.; Rabaey, M., and Neetens, A.: Contribution à l'étude des protéines cristalliniennes par l'électrophorèse, Bull. Soc. belge opht. 104:322-331, 1953.

4. François, J.; Wieme, R.; Rabaey, M., and Neetens, A.: L'électrophorèse sur papier des protéines hydrosolubles du cristallin, Experientia 10: 79-82, 1954.

5. François, J.; Rabaey, M., and Wieme, R. J.: Nouvelle technique de fractionnement des protéines cristalliniennes, Bull. Soc. franç. opht. 67: 26-31, 1954.

6. François, J.; Rabaey, M.; Wieme, R. J., and Neetens, A.: Étude des protéines cristalliniennes hydrosolubles par l'électrophorèse dans la cataracte expérimentale, Ann. Ocul. 187:593-610, 1954.

7. François, J.; Rabaey, M.; Wieme, R. J., and Evens, L.: Étude électrophorétique de l'influence du pH sur les protéines cristalliniennes, Bull. Soc. belge opht. 108:652-659, 1955.

8. François, J.; Wieme, R. J.; Kaminski, M., and Rabaey, M.: Étude des antigènes cristalliniens par les méthodes immuno-chimiques de fractionnement protéinique, Bull. Soc. franç. opht. 68:144-158, 1955.

9. François, J.; Rabaey, M., and Wieme, R. J.: New Method for Fractionation of Lens Proteins, A. M. A. Arch. Ophth. 53:481-486, 1955.

10. François, J., and Rabaey, M., in Discussion on Stemmermann, W.: Deutsche Ophth. Gesellsch. 59:204-207, 1955.

11. Krause, A. C.: The Biochemistry of the Eye, Baltimore, The Johns Hopkins Press, 1934.

12. Mörner, C. T.: Untersuchungen der Proteinsubstanz in den lichtbrechenden Medien des Auges, Ztschr. Physiol. Chem. 18:61-106; 213-222; 233-256, 1894.

13. Schaeffer, A. J., and Murray, J. D.: Amino Acid Composition of the Lens Proteins of the Bovine Eye, Arch. Ophth. 43:1056-1064, 1950.

14. Wieme, R. J., and Rabaey, M.: Les protéines du cristallin et leur rapport avec la cataracte, in 2ième Colloquium St. Jans Hospitaal, Bruges, 1954.

15. Wieme, R. J., and Rabaey, M.: Acquisitions nouvelles dans le fractionnement des protéines du cristallin, in 3e Colloquium St. Jans Hospitaal, Bruges, 1955.

16. Wieme, R. J., and Rabaey, M.: Immuno-Elektrophoretische Untersuchungen über Linsenproteine, Ärztl. Lab. 1:99-100, 1955.

Automatic Intensity Control in Testing Dark Adaptation

RALPH D. GUNKEL, O.D., and HANS BORNSCHEIN, M.D., Bethesda, Md.

In clinical practice quantitative dark adaptation tests are frequently avoided for several reasons. For example, the examination requires more time than the physician is usually able to devote to it, even if he is thoroughly familiar with the instrument and the technique. Since the test is not used routinely, it is difficult either to establish a standard procedure or to have an experienced technician available when needed. Furthermore, the test is of such a nature that much of its value is lost if standard procedures are not followed.

These difficulties have been partly met by developing an apparatus which provides simplification and standardization of the procedures. These improvements were added to the standard Goldmann-Weekers adaptometer, which is the most commonly used modern adaptometer for clinical studies. Besides other advantages, the apparatus includes an arrangement for uniform preadaptation and a self-recording system. The determination of the brightness threshold is made in the usual manner by progressively increasing the intensity of the test light until the subject reports that he sees it. This value, of course, does not represent the true threshold itself but a slightly higher threshold, depending on the rate at which the intensity had been increased. The determination can be made more complete by subsequently decreasing the intensity until the subject reports that he no longer sees the light. The true threshold (correctly defined as a brightness at which the test field is seen with a probability of 0.5) is presumed to lie somewhere between the "threshold of appearance" and the "threshold of disappearance," determined in the manner described above. Usually the mean of both values is regarded as the brightness threshold. To have comparable probabilities of seeing, the rate of increasing and decreasing the intensity should be a uniform one $\left(\frac{d \log I}{dt} = \text{constant}\right)$. This is obviously impossible when the intensity is manipulated by hand and by different persons.

The present study deals with the design of a simple automatic device operating the intensity control of the Goldmann-Weekers adaptometer. The automatization not only provides a better standardization of the test but also reduces the time required of the examiner. In fact, by this method the test can be done as accurately and reliably by a nurse or technician as by the physician himself.

Principle of the Automatic Method

The method utilizes a technique devised by Bekesy [1] for human audiometry and is similar to a method used by Ratliff and Blough [2] in behavioral studies of visual processes in pigeons. The intensity of repeated light flashes is increased automatically until perception occurs. At this moment the subject presses a switch, causing an automatically continuous decrease of the intensity. When perception is completely lost the subject has to switch back to increasing intensity, and so on. The brightness of the test patch is recorded continuously by an ink-writer. The result is a

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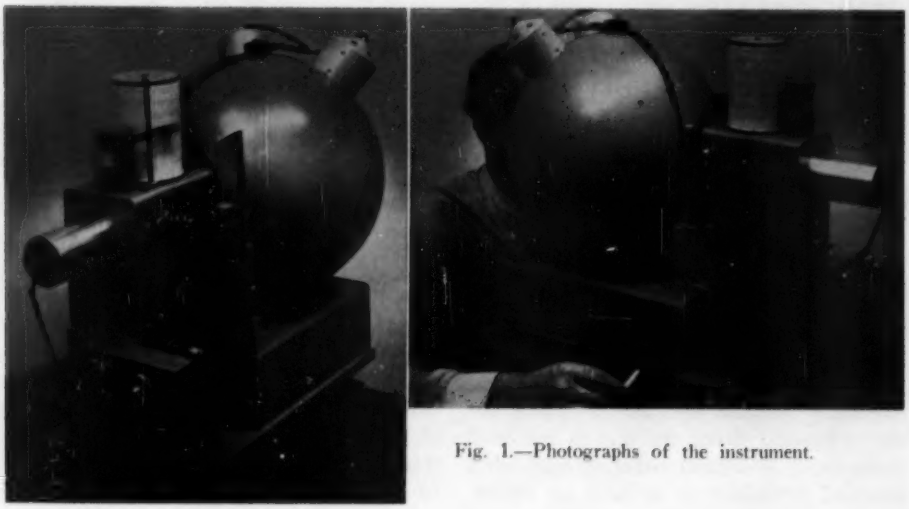

Fig. 1.—Photographs of the instrument.

curve oscillating above and below the threshold.

Apparatus and Procedure

Figure 1 shows the Goldmann-Weekers adaptometer with the modifications introduced in this paper. The original intensity control knob has been replaced by a gear which engages an idler gear which in turn engages a larger gear on the shaft of a 1 rpm Bodine motor. A spring clutch whose tension can be adjusted by means of a knurled nut prevents damage to the motor or mechanism in case the intensity is permitted to run against either stop. A toggle switch directly below the motor permits it to be turned off or on independently of other operations.

A gear ratio has been chosen which changes intensity at the approximate rate of 1.5 logarithmic units per minute. Since the interruptor provided in the adaptometer gives a light-dark ratio of 1:1 with a frequency of 0.5 per second, the intensity difference between any two consecutive flashes will be 0.05 log units.

A toggle switch with an extended handle for easy operation is installed in a convenient location for the subject's right hand. To make it easier for him to remember, raising the switch raises the intensity of the flashing light and lowering the switch lowers the intensity.

In place of the original stylus, which marked the paper by perforation, a tubular pen has been installed, with a small reservoir for ink. Light spring tension holds it against the drum, giving continuous recording of the intensity level.

In cases where the conventional nonautomatic operation is desired, the clutch knob is loosened, permitting the intensity knob to be easily turned by hand. The pen is retracted from the drum and replaced by a stylus which perforates the paper when the examiner wishes.

Before any testing of the brightness threshold, or the series which comprises the dark adaptation curve, it is necessary that the subject be well informed as to his role as a participant, the objectives, and the procedure for the test. Furthermore, a short practice period (without preadaptation) will be found helpful. By way of demonstration, the subject is asked to observe the small red fixation light and the test patch and notice that the latter can be made to appear or disappear by either hand or mechanical manipulation of the intensity control. The subject is easily convinced that the point of appearance is different from the point of

disappearance and that it will require his undivided attention and his best judgment to decide the times of each. He quickly learns to respond automatically by lowering the switch the moment he sees the flashing test patch and raising the switch the moment that it disappears.

To approximate a standard condition of preadaptation, the subject is asked to sit for 10 minutes with his chin in place on the pad of the instrument, his eyes open, the diaphragm slide closed, and both bulbs lighted. This gives a uniform illumination of about 420 millilamberts inside the integrating sphere. During this preadaptation time a new chart can be placed on the drum, the test light calibrated, the pen set in position, and the clutch knob tightened. At the end of the 10 minutes the diaphragm slide is opened, the room lights and preadaptation lights are turned off, and the intensity control motor is turned on. The subject should already have his hand on the reversing switch and be instructed to look only at the fixation light. As soon as he sees any flashing of the test spot he is to press the switch down, which will cause the intensity to gradually decrease. As soon as the last bit of flashing disappears, he raises the switch, which causes the intensity to rise gradually until he again sees flashing, at which time he again lowers the switch. This cycle is repeated constantly for the entire period of the test, which is usually 30 minutes.

The performance of a subject can be checked in progress by observing the illuminated scale below the light meter. If any gross deviations or errors are noticed, the subject can be alerted or advised. If the condition of a patient is such that he becomes too fatigued or confused from watching the fixation light so steadily, the motor may be turned off for about one-minute rest periods every two to five minutes. During these rest periods when the motor is off the pen will trace easily recognizable flat spaces, or plateaus in the otherwise regularly spiked curve. However, it should not be turned off during the first 8 or 10 minutes of the test, since this first part is important for observing the rapid changes incident to the rod-cone break.

If only a measure of the final threshold is desired, and not the complete curve, it can be determined with some saving in time. In this case preadaptation is unnecessary, but the subject should be instructed as before and dark-adapted for at least 15 minutes. Intensity should be set at about the third logarithmic scale for starting, and if the subject does not see the flashing light it should be increased by turning the knob manually. Beginning with the switch down, so that the intensity is decreasing, the test is carried on for about five minutes. If at the end of that time there is no definite downward trend in the curve, this value can be accepted as the approximate threshold. Figure 2 shows sample curves.

Statistical Comparison of Conventional and Automatic Methods

The results obtained with automatic operation were compared with the data resulting from the conventional nonautomatic operation. Subjects were six normal controls and six patients with disturbances of dark adaptation (retinitis pigmentosa, diabetic retinopathy, high myopia, liver disease).

Special precautions were taken with respect to the design of the experiment to avoid bias which may be caused by increasing experience of the subject. In every subject two automatic and two nonautomatic determinations were made. Two tests (separated by an interval of one hour) were executed at the first session (A); the other two tests were given after a pause of one week (B). The combination of tests was varied in the following manner:

(1) A, nonautomatic—automatic; B, reversed sequence
(2) A, automatic—nonautomatic; B, reversed sequence
(3) A, both nonautomatic; B, both automatic
(4) A, both automatic; B, both nonautomatic

The two nonautomatic tests in every subject were conducted independently by two differ-

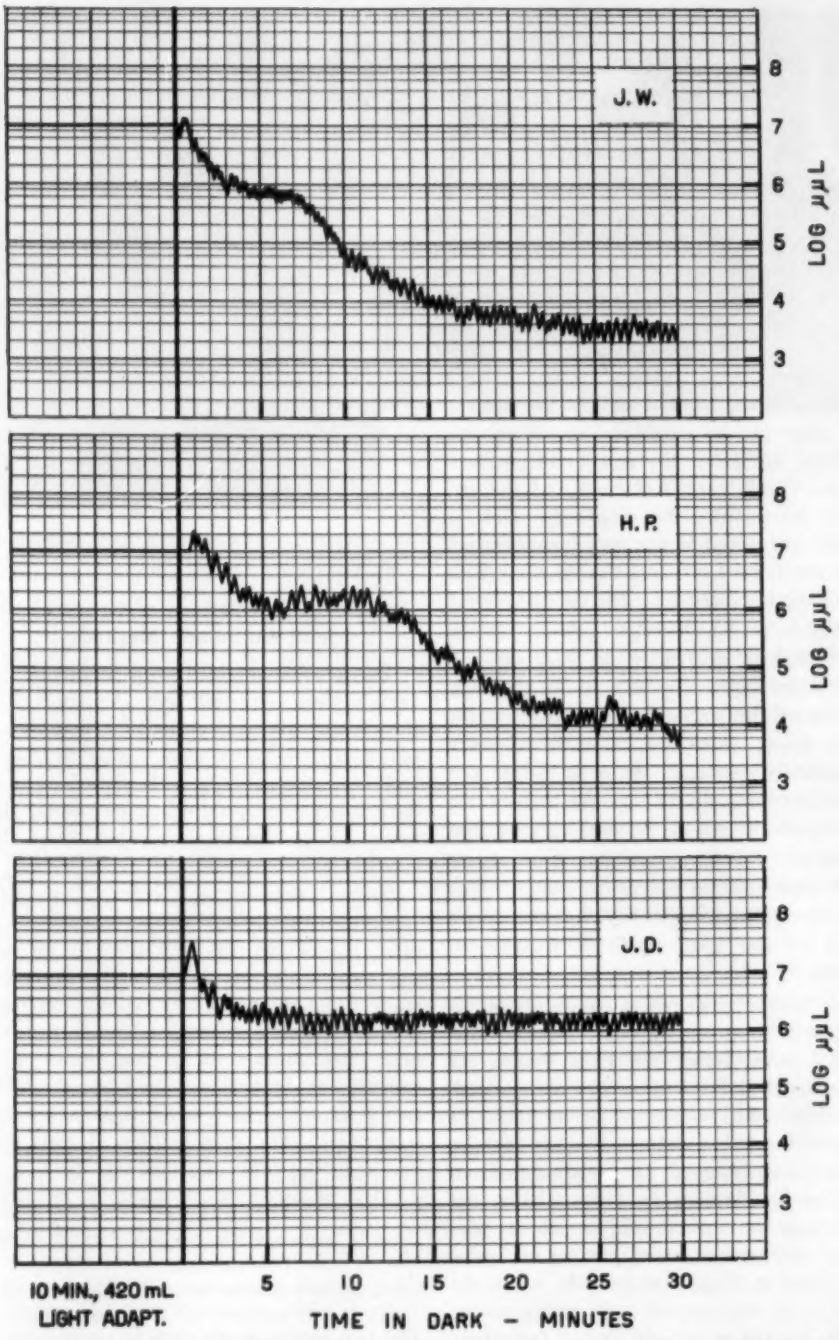

Fig. 2.—Dark adaptation curves recorded with automatic intensity control. J. W., normal; H. P., hemochromatosis; J. D., retinitis pigmentosa.

TABLE 1.—*Comparison of Results with Automatic and Nonautomatic Methods for Twelve Subjects*

Minutes of Dark Adaptation	Mean Threshold Difference (Autom. minus Nonautom.), Log Units	P†
5	−0.016 ± 0.024*	>0.5
12	+0.015 ± 0.033*	>0.5
30	+0.194 ± 0.035*	<0.001

* Standard error of difference.
† P represents the probability of this difference occurring by chance.

ent examiners, neither having seen the results of the other.

With both types of examination the same test conditions were observed: 10 minutes of preadaptation with 420 millilamberts, test patch 11 degrees in diameter with its center 11 degrees below a small red fixation light, and intermittent presentation using the rotating sector. Before every test, an explanation of the procedure was given to the subject, followed by a few minutes of practical training without defined preadaptation.

With the conventional nonautomatic method the threshold of both appearance and disappearance were determined by the examiner every minute during the first 10 minutes in the darkness and every 2½ minutes during the following 20 minutes. The "threshold" curve was drawn through the points representing the logarithmic means of the thresholds of appearance and disappearance. With the automatic method, the subject was allowed to control the intensity by the automatic switching circuit in the manner described before. As in the nonautomatic tests, the threshold curve was recorded for the first 30 minutes of dark adaptation. In a manner analogous to that of the conventional method, "threshold" was defined as the logarithmic mean between the upper and lower limits of the oscillation curve.

As is well known, the dark adaptation curve is composed of two different segments ("cone" segment and "rod" segment) separated by a more or less distinct break after 6 to 10 minutes. The curves obtained with the two different methods were statistically compared at the following characteristic points: (1) 5 minutes (cone segment); (2) 12 minutes (early part of rod segment); (3) 30 minutes (late part of rod segment). As shown in Table 1, a statistically significant difference was evident only for the late part of the rod segment (30 minutes of dark adaptation), where the threshold with the automatic technique was definitely higher than the threshold determined by the conventional technique.

One possible cause for this discrepancy is the fatigue due to the sustained attention required in continuous recording. Another factor to be considered is a change of the adaptation state due to the effect of the test stimulus, since with automatic testing about half of the 900 test stimuli delivered during the 30 minutes of dark adaptation are of suprathreshold intensity. However, they are just barely above the threshold. The problem was investigated in more detail with a well-trained subject. The variation of the final threshold resulting from modifying the procedure is shown in Table 2. With use of the automatic technique, the light stimulus was switched off after 15 minutes of dark adaptation and then presented after 20, 25, and 30 minutes for 1½ minutes at a time. With such dark pauses or rest periods, the final threshold was markedly reduced. However, the threshold failed to decrease if during the periods mentioned above the test stimuli were kept at a con-

TABLE 2.—*Comparison of Results with Standard Procedure and Procedure Modified by Rest Periods**

Automatic			Nonautomatic		
Continuous (Stand. Condit.)	With Rest Periods		With Rest Periods		Continuous
	Light Off	Light On	Light Off (Stand. Condit.)	Light On	
3.65±0.06†	3.38	3.75	3.31±0.06†	3.60	3.60

* Threshold Values in log micromicrolamberts.
† Standard error (three determinations).

stant intensity just above the threshold value (determined just before) with the subject resting and paying no attention to the light. With corresponding modifications of the nonautomatic method analogous results were obtained. The results suggest that the difference in the final thresholds is caused by adaptation effects of the test light rather than by fatigue. Consequently, it should be possible to reduce this difference by shortening the duration of the light flashes. However, except in comparing directly the results obtained by different methods, a small but systematic threshold increase of about 0.2 log units is a negligible factor in clinical application of the technique.

Comments and Conclusions

In practical use the automatic method of threshold determination as adapted to the Goldmann-Weekers instrument has shown some advantages compared with the conventional technique. The automatic control of intensity provides better standardization of the test. Furthermore, the dark adaptation curves continuously recorded in this way show considerably more detail. Above all, the "break" can be determined more exactly, which may be of interest in certain pathological cases in which a delay is characteristic. The width of the oscillation curve represents additional information with respect to reliability.

Previous fears that the technique would involve too much effort for the patient have not been confirmed. With one exception, every subject preferred the automatic method to the nonautomatic one. Nevertheless, the possibility remains that with extremely passive patients some difficulties may arise, manifested by marked irregularities of the recorded curve. In such cases the conventional technique, with its element of personal supervision by the examiner, may give better results. It is made available simply by switching off the automatic intensity control.

In almost every case, the automatic method makes possible the recording of a reliable dark adaptation curve by a nurse or technician even in the absence of the examining physician. Consequently, dark adaptation tests are clinically applicable in more cases than have hitherto been possible.

National Institute of Neurological Diseases and Blindness.

REFERENCES

1. Bekesy, G.: A New Audiometer, Acta otolaryng. 35:411, 1947.

2. Ratliff, F., and Blough, D. S.: Behavioral Studies of Visual Processes in the Pigeon, Office of Naval Research, Technical Report, Project NR 140-072, Psychology Laboratory, Harvard University, Cambridge, Mass., Harvard University Press, 1954.

Modification of the Friedenwald-Kinsey Formula of Intraocular Pressure

JULIUS KESSLER, M.D., New York

The formula of the intraocular pressure proposed by Friedenwald and Kinsey is the following:

$$IOP = k(Cap\ P + OP_{Aq} - OP_{P1})$$

where

$$k = \frac{k_{in}}{k_{in} + k_{out}}$$

The values k_{in} and k_{out} are the effectiveness with which the osmotic and hydrostatic forces are converted into intraocular pressure.[1] The pressure of the episcleral veins has to be considered in outflow only, but not in expressing the intraocular pressure itself.[2]

It seems that the effectiveness with which the osmotic and hydrostatic forces are converted into intraocular pressure is based upon their influence on inflow and outflow. The formula of the intraocular pressure can be regarded as derived from an equation of inflow and outflow, where k_{in} and k_{out} are coefficients of flow. The terms k_{in} and k_{out} are the volumes of water transferred within one minute by a pressure of 1 mm. Hg through the blood-aqueous barrier or through the ways of outflow, respectively. In an equation of inflow and outflow the episcleral venous pressure should be considered.

In steady state the inflow is equal to the outflow:

$$(Cap\ P + OP_{Aq} - OP_{P1} - IOP)k_{in} = (IOP - VP)k_{out}$$

Derived from this equation, the intraocular pressure is

$$IOP = (Cap\ P + OP_{Aq} - OP_{P1})k + VP(1-k)$$

As seen in this modification of the formula of Friedenwald and Kinsey by introduction of the episcleral venous pressure, the intraocular pressure consists of two parts, the second part, $VP(1-k)$, being in the normal eye almost as high as the episcleral venous pressure. More than half of the normal intraocular pressure seems to be due to the episcleral venous pressure.

As seen from this equation, changes of k_{out}, k_{in}, Cap P, and $OP_{Aq} - OP_{P1}$ will produce greater changes of intraocular pressure in eyes with high tension than in normal eyes. Reduction of $OP_{Aq} - OP_{P1}$ to half its value will reduce the first part of the intraocular pressure to about half its value, and that would mean in a normal eye with an intraocular pressure of 16 mm. Hg a reduction by about 3 mm. Hg, that is, by about one-fifth of its value, while in an eye with an intraocular pressure of 50 mm. Hg it would mean a reduction by about 20 mm. Hg, that is, almost by half its value. According to the original formula of Friedenwald and Kinsey, a reduction by about half its value would be expected also in the normal eye, in contradiction to experience.

The episcleral venous pressure acts like a valve at the outflow, keeping the intraocular pressure above a basic value of about 10 mm. Hg. According to the modified equation, the intraocular pressure in the normal eye will change by about the same value as the episcleral venous pressure does, since $1-k$ is only slightly different from 1 in the normal eye.

For most of the factors of the equation there are measurements or estimations of the average normal values. The average normal k_{in} can be estimated from these values to be about 0.15. This value permits an estimation of the value of the normal average fluid exchange:

$$(OP_{P1} + IOP + H_2O\ D.P.)k_{in}$$

H_2O D. P. is the active diffusional pressure of water. Friedenwald considered the whole

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diffusional pressure of water of nearly 1,000,000 mm. Hg as active in the transfer of water.[1] The value of the fluid exchange by this pressure would be beyond reasonable expectance and in no relation with experimental findings. Other factors are considered to explain the discrepancy. A pressure near 1,000,000 mm. Hg would be necessary to keep the water molecules in the volume they fill, if they were free as in a gas. Actually, the atmospheric pressure is sufficient a force to keep the molecules of fluid water in the volume they fill, the rest of the diffusional force of the water molecules being balanced by the forces of attraction of the molecular dipoles. The active diffusional pressure of water, H_2O D. P., is equal to the atmospheric pressure, and a force of this size only is active in driving water through a membrane. $OP_{P1}+IOP+H_2O$ D. P. being about 6000 mm. Hg, the normal average volume of exchange fluid would be about 90 cu. mm. per minute. Actually, the size of this volume could be changed by other factors. The value is in good agreement with the values found by experiment.

Summary

An alteration of the formula of the intraocular pressure of Friedenwald and Kinsey is suggested and discussed.

229 E. 79th St. (21).

REFERENCES

1. Kinsey, V. E.: A Unified Concept of Aqueous Humor Dynamics and the Maintenance of Intraocular Pressure: An Elaboration of the Secretion-Diffusion Theory, Arch. Ophth. 44:215, 1950.

2. Kinsey, V. E.: Personal communication to the author.

Carcinomas in the Region of the Lacrimal Sac

EDMUND B. SPAETH, M.D., Philadelphia

A discussion of malignancy of the lacrimal sac is disregarded almost entirely in textbooks on pathology, regardless of whether these be on general pathology or related wholly to ophthalmic pathology. One such textbook states: "Carcinoma of the tear sac is rarely primary, usually secondary, infiltrative from the paranasal sinus, and may also appear as adenocarcinoma." In contradistinction, I have never found a certain secondary carcinoma; all were primary, and none arose from the nasal accessory sinuses. Extension from the lacrimal sac to the sinuses is the common sequence, never the opposite. One can hardly consider a case to be malignancy of the lacrimal sac when this is a part of tremendous orbital and periorbital extension, originating elsewhere.

If it were not for Duke-Elder's [1] consideration of this subject, one might think the condition rare. I have had, up to this present moment, seven cases of malignancy of the lacrimal sac. Two of these were of the squamous-cell type; the remainder, of the basal-cell type of malignancy. At this time, two of these patients are known to have died, as the result of the malignancy. Two have disappeared; that is, all track has been lost of them, though it was known that they had had a recovery, in each instance, of two years. One case, also with a two-year recovery, is now under active treatment for the plastic defect connected with the surgery necessary for the excision of the malignancy.

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The Wills Eye Hospital and the Graduate Hospital, the Graduate School of Medicine, University of Pennsylvania.

First, a comment as to the cytology of this malignancy, for it is variable. The tumor cells may be of a squamous- or of a basal-cell type; a cylindrical-cell epithelioma was described by one author; another author had one case of a transitional-cell type, and three adenocarcinomata have been reported. The only certainty relative to this is that the type of malignant cell cannot be known before the operation.

Stock [2] described, in addition to cysts of the lacrimal sac, fibroma, carcinoma, sarcoma, lymphoma, and plasmoma.

The manner in which the lacrimal sac becomes involved is not certain. One must consider the possibility of a papilloma as the precursor of the malignancy. Papillomata are not rare. Many cases have been reported, and the tendency which papillomata have to change into malignant lesions is well known.[3] Hildén stated that cell metaplasia is outstanding in significance or etiology in malignancy of the lacrimal sac in this relationship to papilloma. It is also known that this changeover may be delayed for a very long time. Dupuy-Dutemps [4] reported one case in which malignant degeneration occurred 25 years after its recognition (the relationship is assumed).

The second possibility as to etiology is the possibility of extension of epithelial-cell malignancy from the conjunctiva through one or both of the canaliculae and inevitably the involvement of the mucosa of the sac itself. If this does occur, one can hardly speak of such a case as a primary malignancy of the sac itself. Two of the three cases to be presented here may be concerned with this possibility. One case, when first seen, had involvement of the conjunctiva of the inner canthal angle, extension of this on to the lid surface, and

extension of the malignancy across the epithelial surface of the inner canthal angle into the prelacrimal region, on to the side of the bridge of the nose, and penetrating into the lacrimal fossa, involving the entire membranous lacrimal sac (Fig. 1). The patient stated, however, that prior to the external ulceration present at the time of his first visit there had been a hard lump in the lacrimal region for some time, at least for a number of months. It is impossible to say whether this malignancy arose externally and penetrated subsequently or whether the primary origin was in the sac proper and extended externally.

The second case related to this etiological possibility was first referred for surgery because of a prelacrimal fistula. This case also had an involvement, by extension, into the canaliculae, because the reoperation necessary showed a recurrence within the inferior canaliculus and the tissues of the lid at the inner canthal angle. A likely course of events in this case was that the involvement was primary in the mucosa of the sac, an extension through to the surface was the cause of the fistula, and the secondary operation was necessary because of the incomplete removal of malignancy at the time of the primary surgery, this being present, however, at that time.

The third etiological possibility is that a chronic dacryocystitis of long standing might be the "precursor," as Duke-Elder words it. Rollet [5] felt this was probable, and Schweig [6] and, even earlier, Dalén [7] described carcinomata arising within the remains of a sac following dacryocystectomy. In both of these instances cited, the dacryocystitis present might have been a secondary infection, an accompaniment of the malignancy, and the appearance of the malignancy might have resulted not from incomplete sac extirpation and carcinomatous degeneration of the remains of the sac but from primary malignancy of the sac with subsequent secondary purulent dacryocystitis—the cystectomy having failed to remove all of the carcinomatous involvement.

Regardless of the exact basic situations present, it is possible that many of these cases had had, earlier in their course, epiphora, a palpable mass, and, subsequently, ulceration and that early in their course these cases were thought to be dacryocystitis.

In Rollet's three cases of malignancy of the lacrimal sac, only one of which was a carcinoma, he described that case as having had a soft neoplastic enlargement of the lacrimal sac, with epiphora and with a suppurative discharge.

Dalén, in discussing his case, stated "One can believe with certainty that the carcinoma did not arise from the mucous membrane of the sac but from the residuals of the lacrimal sac left following incomplete extirpation; the malignancy was resected from deep within the dacryocystectomy scar; that the superficial layers of skin overlying the scar were dragged into the scar; that the carcinomatous metaplasia occurred at this place."

There is no doubt whatsoever that malignancy occurs as a result of chronic irritation. There are many instances through the entire field of oncology to prove this conclusively. There is some doubt, however, whether a bacterial suppurative process, no matter how long this may be present, ever results in malignant metaplasia. It almost seems as if a primary suppurative process protects against malignancy of those tissues involved. Surgical clinicians other than ophthalmologists have also thought this to be a likelihood.

The complications which have appeared in my cases included incomplete removal, confirmed histologically, making further immediate extensive surgery imperative; recurrences into the lower lid, making reoperation necessary, though at a later date, several months after the primary operation; involvement of the bony lacrimal fossa with extension into the nose, the ethmoid sinus, the maxillary sinus, and the orbit.

The cause of death in the two cases known to have terminated fatally was continued extension and penetration intracranially.

It is proper to mention at this point two cases of extensive orbital evisceration, to refute a statement, made earlier herein, as to etiology. Soft tissue and bone removal—including the lacrimal sac, the lacrimal fossa, and the entire ethmoid sinus—was made obligatory because of extension of malignancy into the orbit from epithelioma which had first appeared in the soft tissues of the lower lid. In one of these cases the extension of the malignancy continued downward along the bony lacrimal-nasal canal, posterior to the sac, and into the orbit, but the malignancy did not enter into the sac itself. The postoperative dissection of both the blocks of tissue exenterated showed failure to penetrate into the sac.

Spratt [8,9] called attention to adenopathy in the submaxillary lymph nodes. I have seen preauricular and superficial cervical adenopathy, but involvement of the submaxillary lymph nodes is rare, though submaxillary lymph node extensions have been seen repeatedly in adenocarcinoma of both upper and lower lids.

Some of the comments which Spratt made in his analysis of 16 cases from the literature are rather interesting. The following are significant: "Since the diagnosis of the malignant nature was made in only one case . . . prior to operation, removal was incomplete and recurrence was the rule." ". . . the onset is insidious, with . . . symptoms no different from those of an ordinary cystic condition of the lacrimal sac." "A tumor gives rise to epiphora owing to pressure of the thickened wall of the lacrimal sac. Pressure on the sac causes little or no regurgitation, and the duct is patent on irrigation and on probing." "In the third, or final, stage, characterized by rapid growth . . . of the preauricular and the maxillary lymph glands, the growth presents little difficulty in diagnosis."

Fig. 1.—Left, patient at the time of admission. Right, following primary radical surgery. Recurrence at lip of wound.

Fig. 2.—Condition following radical surgery. Complete, permanent recovery.

Report of Cases

Case 1.—A man, aged 70 (Fig. 1), was referred because of a very evident epithelioma at the inner canthal angle of the right eye, with a fistula from the lacrimal sac into the nose along the lacrimal-nasal duct. The surgery done was an immediate evisceration of the orbit, with removal of the medial wall of the orbit, including the area of the lacrimal-nasal duct, the lacrimal fossa, and the ethmoid bone. The patient made an uneventful recovery from the surgery. The diagnosis was a basal-cell carcinoma. This surgery was followed by x-ray therapy thought to be adequate in dosage and in extent of application. A year later there was a recurrence of malignancy in the medial edge of the site originally operated on. One can see this in the second photograph of Figure 1. This malignancy had penetrated into the surgical defect on its medial wall, into the roof of the orbit, and very likely intracranially. The patient was given further extensive x-ray therapy to a maximum amount. The malignancy continued to advance, however, and the pa-

tient is known to have died several months later.

Case 2.—A woman was 54 years old at the time of her first visit. The patient had an obstructive suppurative dacryocystitis, with a hard indurated mass in the lacrimal area. A dacryocystectomy showed malignancy, of the squamous-cell type. The surgery was followed by x-ray therapy. There was a recurrence a year later. The second surgical procedure was an orbital evisceration, with complete removal of the bony lacrimal-nasal duct into the nose. The exenteration included also the lacrimal fossa and a goodly portion of the ethmoid. Figure 2 illustrates the surgical appearance. Further x-ray therapy followed this surgery. The patient has, at the present time, remained cured for a period longer than five years. Her plastic defect is minimized by a prosthesis (Fig. 3).

Case 3.—A young man, aged 38, was referred with a diagnosis of chronic suppurative dacryocystitis with a fistula. In this instance the diagnosis of carcinoma was made preoperatively from the history of the case and from the gross appearance. The immediate surgery done was a radical extirpation of the prelacrimal region, including the inner half of the upper and the lower lids and the bony lacrimal fossa. The lacrimal-nasal duct was opened along its entire length and resected. The area was grafted flat with a skin graft, razor cut. At the same time, a tarsorrhaphy was done of the remaining portions of the upper and lower lids to protect the cornea from exposure. A year later, prior to the correction of the plastic defect, a small rough area was dis-

Fig. 3.—Patient wearing her prosthesis.

Fig. 4.—After primary resection of malignancy, primary grafting, tarsorrhaphy of remaining structures of lids.

covered along the edge, anterior and medially, at the junction of the graft and original skin. This was resected and examined histologically. No further malignancy was found.

The first attempt to correct the plastic defect was unsuccessful. This consisted of the burial of a mucous membrane graft into the forehead for subsequent use as a mucous membrane epithelial flap. This flap was moved into a correcting position and sutured into the surgical defect. There was an extensive slough, however, along the medial margin of the flap. It was necessary to return this flap to the forehead and to remove and discard the mucous membrane. The scarring seen on the forehead in Figure 4 is the result of that abortive attempt. Figure 4 also shows the surgical defect and the results of the skin grafting. A year later a second attempt was started for the correction of the plastic defect. The patient was circumcised (by a urologist), and a portion of the mucous membrane obtained was grafted flat beneath the skin overlying the maxilla so that it would form the posterior surface of a pedicle flap to be raised later. This second step was done two weeks after the first stage. Figure 5 shows this in position. Figure 6 is the present appearance. Further plastic surgery is necessary and will be done shortly. This will be relatively minor compared to that which has been carried out up to the present time.

Fig. 5.—Pedicle flap from face, posterior surface lined with prepuce mucous membrane. Forehead scar referred to in text.

Fig. 6.—Side view of scar from pedicle flap. Visual acuity with correction 6/7.5.

The remaining four cases seen were not unlike these described. One of the deaths (known deaths) was similar to the second case seen; in this instance the death followed a third operation, a second recurrence—a total time interval from first operation to death of three years. The remaining three cases not presented in detail were all of lesser primary involvement; one had what was considered to be a recurrence at the edge of the initial extirpation scar, but the histological examination of the tissue removed did not confirm that, and, as stated earlier, only two of these cases are known to be permanently cured.

Conclusions

The etiology, as regards the source of the malignancy, is in doubt; there may be a primary onset, within the mucosa of the sac itself, and a second, an extension from the conjunctiva. The course of this condition, on the basis of my cases and illustrated by three patients described in some detail, suggests the following essentials in the treatment:

1. Early diagnosis.

2. Extensive primary surgery, including removal of the prelacrimal region, the inner canthal angle of the lids, and the bony and membranous lacrimal-nasal canal.

3. One of the most important parts of this surgery is that the lacrimal-nasal duct be opened in its entire length so that is can be inspected and resected, as is necessary.

4. If there is a recurrence, secondary surgery must be a complete evisceration of the orbital contents and of all contiguous areas possibly involved. Careful histologic examinations are necessary to check upon and assure the thoroughness of this surgical extirpation.

5. The plastic surgical correction should not be done until such time has elapsed that one may be certain that further recurrences will not appear.

6. X-ray therapy is a necessary adjunct for proper treatment.

The principles connected with the plastic correction are not new, these being well known and well established. The high incidence of mortality in these cases seems to indicate that bold surgery is necessary if a recovery is to be obtained.

1930 Chestnut St. (3).

REFERENCES

1. Duke-Elder, W.: Textbook of Ophthalmology: Vol. 5, St. Louis, The C. V. Mosby Company, 1952, p. 5352.

2. Stock, in Handbuch der gesamten Augenheilkunde, edited by T. Saemisch, Leipzig, W. Englemann, 1910, Vol. 1, Pt. 1.

3. Hildén, B.: Klin. Monatsbl. Augenh. 82:661, 1929.

4. Dupuy-Dutemps, L.: Bull. Soc. franç. opht. 42:215, 1929.

5. Rollet: Arch. opht. 26:337, 1906.

6. Schweig: Klin. oczna 16:200, 1938; quoted by Duke-Elder[1] p. 5354.

7. Dalén, A.: Beitr. Augenh. 41:1, 1899.

8. Spratt, C. N.: Arch. Ophth. 18:267, 1937.

9. Spratt, C. N.: Arch. Ophth. 24:1237, 1940.

Orbital Metastasis of Renal Carcinoma

C. E. VAN ARNAM, M.D., and MAX FINE, M.D., San Francisco

The appearance of metastatic carcinoma in the orbit from a remote source is of such unusual occurrence as to excite special interest. Reports of metastases from adenocarcinoma of the kidney parenchyma have been particularly infrequent. One case to be presented represents a common manifestation of metastatic disease in the orbit by its invasions from the sinus with functional loss of the eye. The second case represents an unusual manifestation by its appearance in the skin on the orbital margin.

Renal carcinoma is known by a variety of names: hypernephroma, carcinoma, adenocarcinoma of the parenchyma, Grawitz tumor, and clear-cell carcinoma. Its curious characteristics and fickle natural history account for this varied nomenclature and the continued confusion in the literature over its origin and identification. It may be either slowly or rapidly growing. It is locally invasive and characteristically metastasizes via the blood stream because of its tendency to invade the veins of the kidney pedicle. By this route tumors of varying size may shower the body with metastatic emboli. A distant lesion may herald the presence of a silent carcinoma of the kidney of large size and unknown duration. Multiple secondary lesions are common, occurring at intervals, varying from months to years, after the primary tumor has been removed.[7] Widely scattered minute foci in the lungs have been noted, in which no activity could be demonstrated.[4]

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From the Department of Surgery, Veterans Administration Hospital, San Francisco, and the Department of Ophthalmology, Stanford University School of Medicine.

Why metastases appear late or not at all when the body is showered with tumor cells remains a mystery. Multiple tumor emboli do not necessarily mean multiple metastatic foci. Removal of a solitary primary tumor, even when detected by a distant metastasis, has increased a life span.[6]

CASE 1.—A rancher was 59 years old when admitted for the first time to the Oakland Veterans Administration Hospital, in August, 1953, with a complaint of bleeding from the right side of the nose and diminished visual acuity in the right eye. Four such episodes of bleeding had occurred in the previous eight months. Visual symptoms had been present six months.

Past history revealed a complaint of gross hematuria and right-sided abdominal pain in April, 1948. A complete urinary tract investigation in another hospital had failed to reveal the cause. In December, 1949, twenty-one months after the first symptoms, he was again admitted to the same hospital because of recurrent gross painless hematuria. Pyelograms demonstrated elongation

Fig. 1 (Case 1).—Photograph of the patient taken in March, 1955, after the second course of x-ray therapy. Here is shown the tumor mass encroaching on the right orbit from the medial side, displacing the globe downward and laterally. Loss of function of the eye is apparent.

and deformity of three minor calices in the midportion of the right kidney characteristic of a space-occupying lesion. A right nephrectomy was performed in January, 1950. A 4 cm. tumor with an intact capsule was found in the midanterior surface of the kidney. There were no palpable nodes in the area of the pedicle. Diagnosis was adenocarcinoma of the kidney, primary (Figs. 3 and 4).

On the patient's admission to the Oakland Veterans Administration Hospital in 1953, nasal bleeding had persisted for two weeks after biopsy of the right middle turbinate in a search for the cause of his recurrent epistaxis. The vision in the right eye was hand motion; in the left eye, 20/20. The right eye was impaired in its upward and medial rotations. Exophthalmometer reading was 18 mm. on the right and 15 mm. on the left. A large dense central scotoma was present in the right eye. The fundi showed early senile degenerative changes in the macula of the right eye, with clear media and moderate arteriosclerotic retinopathy in both eyes. Skull films revealed destruction of the ethmoid cells on the right (Fig. 2), clouding of the sphenoid sinus, and erosion of the base of the skull, involving the lesser wing of the sphenoid bone. A diagnosis of neoplasm of the right ethmoid sinus with pansinusitis on the right was made. One month after admission proptosis had advanced from 3 mm. to 9 mm.

In December, 1953, exenteration of the right ethmoid sinus was carried out by external approach to the ethmoid area with a curvilinear incision parallel to the brow. When the periosteum over the lamina papyracea was reflected, there was exposed a 2 by 2 cm. mass, bluish-brown, which ruptured into the orbit. Frozen sections revealed only inflammatory tissue. A partial excision of the mass was effected, and a second biopsy specimen was taken, in which adenocarcinoma of the kidney was reported (Figs. 5 and 6).

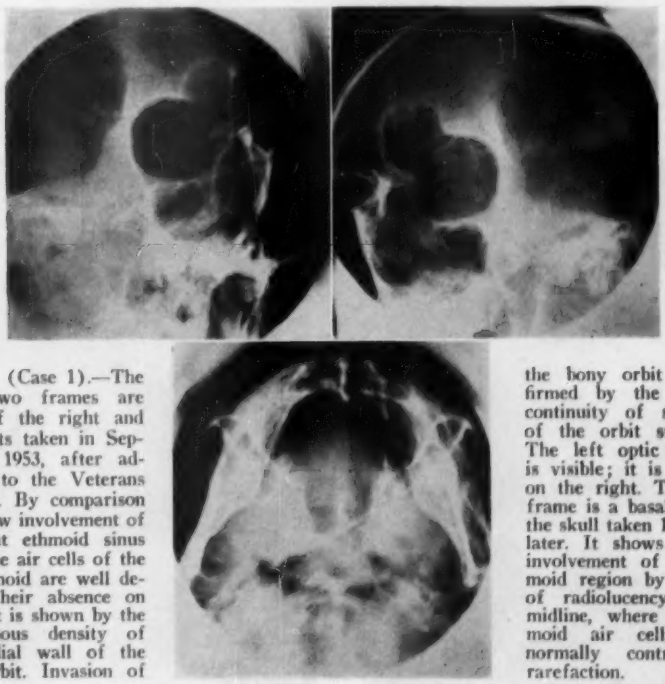


Fig. 2 (Case 1).—The upper two frames are views of the right and left orbits taken in September, 1953, after admission to the Veterans Hospital. By comparison they show involvement of the right ethmoid sinus only. The air cells of the left ethmoid are well defined. Their absence on the right is shown by the homogenous density of the medial wall of the right orbit. Invasion of the bony orbit is confirmed by the loss of continuity of structures of the orbit superiorly. The left optic foramen is visible; it is obscured on the right. The lower frame is a basal view of the skull taken 18 months later. It shows bilateral involvement of the ethmoid region by the loss of radiolucency in the midline, where the ethmoid air cells would normally contribute a rarefaction.

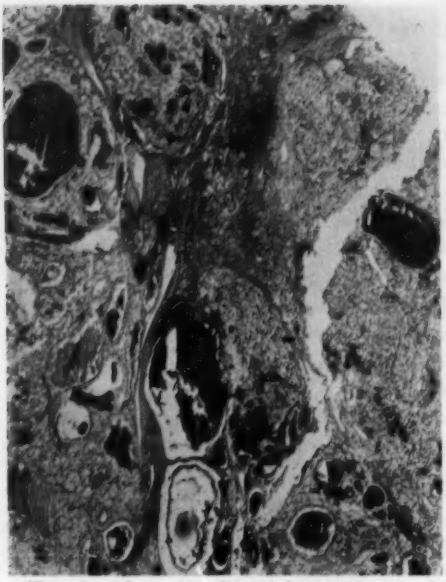


Fig. 3 (Case 1).—Photomicrograph of the original tumor removed with the right kidney in January, 1950, showing the characteristic pattern of clear cells distributed in sheets and cords with a tendency to simulate tubule formation. The vascularity of the tumor is confirmed by the presence of blood residues throughout the spaces in the tumor section. This same appearance is also interpreted as cells arranged about venous sinuses. Reduced from mag. × 21.

Fig. 4 (Case 1).—High-power view of the section shown in Figure 3, showing the loose structure composed of foam cells and the attempt at tubule formation. Blood residues are evident, some within tubules. Reduced from mag. × 110.

Fig. 5 (Case 1).—Specimen taken from the orbit. There are solid alveoli of clear cells consisting of a mass of tube-like structures filled with a coagulum of proteinaceous material. There are also visible some spicules of bone and epithelial elements from the sinus from which it was taken. Reduced from mag. × 21.

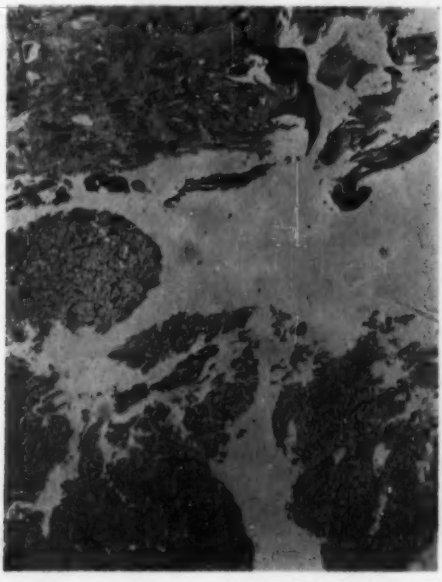
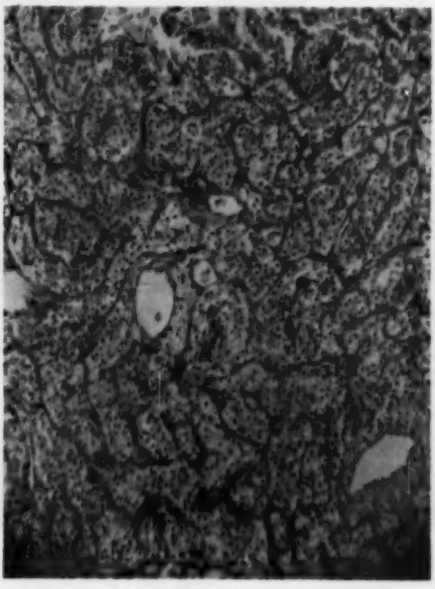


Fig. 6 (Case 1).—Higher magnification of the specimen of Figure 5, showing the large size of the cells lining the tubules. The cytoplasm is remarkably clear and without structural detail. The nuclei are small and usually arranged against the basement membrane. Reduced from mag. × 110.



A bone survey following this surgery revealed an osteolytic lesion of the inferior portion of the left obturator ring. In view of this second metastatic locus, radical sinus surgery was deferred in favor of x-ray irradiation. Accordingly, the patient received 3000 r over a four-week period through right orbital and left nasal ports.

During the next year he was hospitalized three times to receive supportive treatment for profuse hemorrhage from the nose. In February, 1955, he was again admitted for palliative x-ray therapy, receiving 4000 r in the same region. Vision in the right eye was reduced to light perception. Secondary optic atrophy was evident. The eye was markedly proptosed and displaced laterally and inferiorly (Fig. 1). A mass was visible in the right nasal passage and the nasopharynx. The anterior portion of the mass was visibly pulsatile.

The patient was again admitted to the hospital in July, 1955, for control of bleeding. In the next four months he suffered five such episodes of bleeding from the nose requiring dramatic efforts to control, including blood transfusion and ligation of the right external carotid artery. On Dec. 6 a second external ethmoidectomy was elected by the same route in a further attempt to control hemorrhage. The tumor was found to have invaded the opposite ethmoid, the sphenoid sinus, and the cribriform plate to the anterior fossa. At the base of the skull a communication with the cranial cavity was found through which an instrument could be passed. The greater mass of the tumor was removed from the nose in pieces. The patient died on the 12th postoperative day. At autopsy metastases were found in the left kidney, adrenals, liver, and skull. No involvement of the lungs was demonstrated.

Comment.—There are few recorded cases of renal carcinoma metastastic to the paranasal sinuses. Biendara summarized 12 cases from the literature dating from 1905 to 1951.

The usual presenting symptoms are nasal bleeding and obstruction of the nasal passage causing difficult breathing. Occasionally a swelling on the face arises by extension from the sinuses. A mass is often visible in the nose, and a presumptive diagnosis of polyp is made. Severe symptoms can result from even small tumors. Symptoms of a single metastatic focus may precede knowledge of the primary tumor. Pulsation of the mass in the nasal cavity has been a common finding.

Invasion of the orbit occurs when the slowly growing tumors extend from the neighboring sinuses. Damage to the eye follows.

In many cases therapy is palliative when there is widespread involvement. Treatment has included x-ray, radium, attempts at surgical excision, and ligation of the external

Fig. 7 (Case 2).—Frontal view of the patient, demonstrating the clinically obtrusive lesion and showing its position in the eyebrow. Its isolation in the skin is suggested by the protrusion and the stalk-like configuration.

Fig. 8 (Case 2).—Side view of the lesion, showing the degree to which it projects forward. The character of the surface of the tumor is demonstrated well.

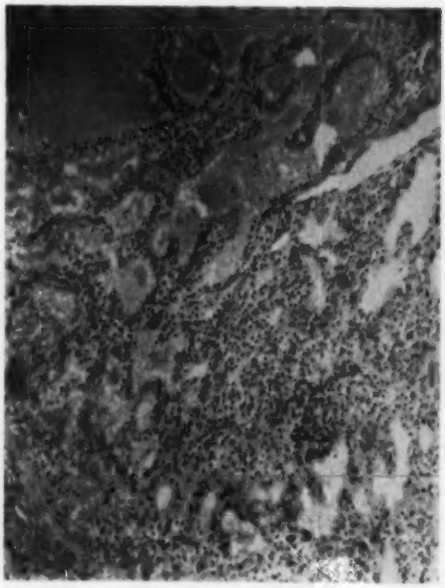
carotid arteries for control of recurrent hemorrhage. Local excision may effect a cure when the tumor is discovered early and found to be well isolated. Surgery by the external approach is advised because of the better visibility and ease of controlling bleeding which it affords. In the cases reported the over-all result was dismal.

Case 2.—A 72-year-old retired farm laborer was admitted to the San Francisco Veterans Administration Hospital in August, 1955, with a complaint of chronic pain in the low back radiating into the hips. Past history revealed that he had been admitted to another hospital in 1947 with a complaint of hematuria of five months' duration. He subsequently underwent an operation for a mass in the left side of the abdomen. A tumor involving the greater portion of the left kidney was discovered, necessitating extirpation of that organ. The tumor, a carcinoma of the kidney parenchyma, was presumed eradicated (Figs. 9 and 10). Recovery was uneventful.

The patient was admitted yearly to the same hospital for follow-up care, excepting the years 1950 and 1952. X-rays of the chest and abdomen taken on each admission were negative for local recurrence or evidence of metastatic spread until November, 1954, seven years after the primary tumor had been removed. At this time a coin-shaped lesion was revealed in the lower lobe of the left lung. Demineralization of thoracic and lumbar vertebrae was also noted.

X-rays taken on admission to the Veterans Hospital verified the spinal lesions to have advanced and the lesion in the lung to have increased in size from 14 mm. to 27 mm. The patient was seen in the eye

Fig. 9 (Case 2).—Photomicrograph of the primary tumor removed with the left kidney in 1947. This slide shows the most frequent microscopic picture of carcinoma of the kidney. The characteristic pattern of clear cells arranged in sheets and cords is well demonstrated. Reduced from mag. × 110.



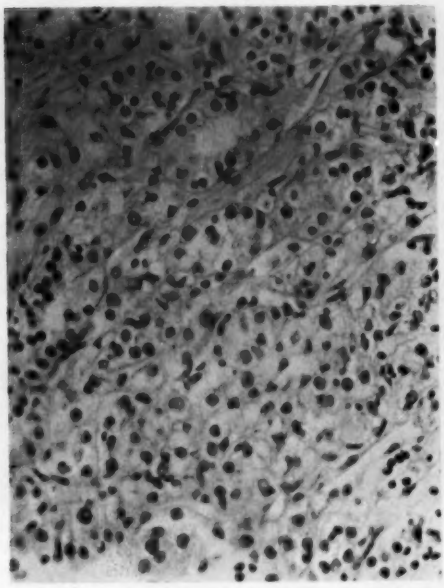


Fig. 10 (Case 2).—High-power view of the section shown in Figure 9. The clear structure is largely due to hydropic change in the cytoplasm and to a lesser degree to the accumulation of fat. It is not a degenerative process, since it occurs in areas well supplied with blood and is not related to necrosis. Reduced from mag. × 400.

clinic on referral from the medical service with a complaint of poor vision and difficulty in wearing his glasses due to the obstruction presented by a tumor on the right eyebrow. The patient stated that the tumor had developed suddenly from a small papule in the eyebrow and had been present only four months. It had gradually increased to its present dimensions of 9 by 15 mm. (Figs. 7 and 8). There had been no pain. He had never been fitted with glasses for an aphakic right eye. The vision of this eye could be corrected to 20/25. Vision in the left eye was reduced to 20/60, owing to an immature senile cataract. The remainder of the eye examination was negative except for the growth on the right eyebrow. The tumor arose from the surrounding area as though it had mushroomed through the skin. There was minimal increase in vascularity in the skin at its base. The tumor pulsated when the skin at the base was put under tension, indicating a large subcutaneous arterial supply. It was moderately firm, freely movable with the skin and nontender. The color was bluish-red; the surface, irregular, and it resembled a hemangioma. A diagnosis of metastatic kidney tumor or hemangioma was made. The tumor was excised without difficulty. On section of the gross specimen, the cut surface was pale yellow and firm. The apparent vascular nature was not evident until tissue sections were made (Figs. 11, 12, 13).

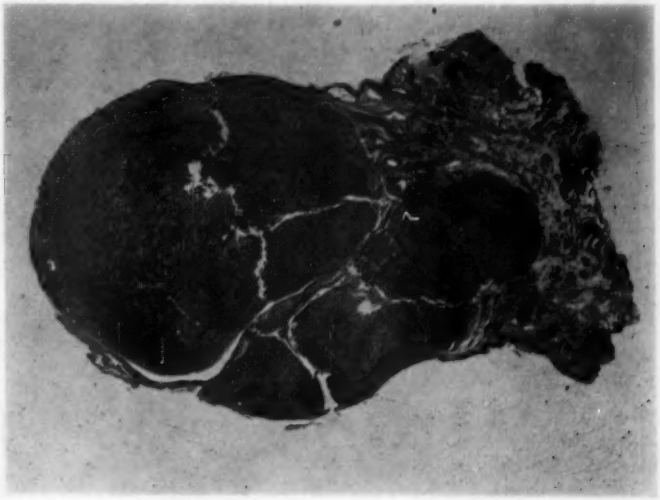


Fig. 11 (Case 2).—A longitudinal section of the lesion excised from the brow, demonstrating the subcutaneous tissue to be free of tumor. The vascularity of the tumor is notable. Reduced slightly from mag. × 5.

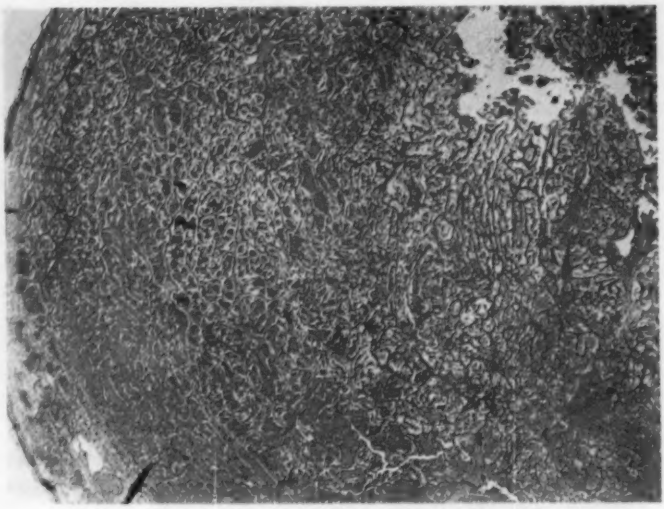


Fig. 12 (Case 2).—A low-power view of the metastatic lesion. The presence of large amounts of blood within the tubule formation as demonstrated here supports the contention of some writers that the tumor may arise from vascular elements. The view generally held is that the tumor has its origin from tubular elements of the parenchyma. Reduced slightly from mag. × 21.

Comment.—Cutaneous and subcutaneous manifestations of kidney carcinoma do not always appear the same. They may simulate lymphoma,[3] a sebaceous cyst, adenopathy, or a hemangioma. Malignant nodules under or in the skin are characteristically firm or hard, discrete, and at first freely movable in relation to the deep fascia. They often appear suddenly and grow rapidly for a time, rarely exceeding 3 to 4 cm. in diameter, before their growth becomes arrested. While they are small, the skin overlying them remains normal in color and often free from attachment to the malignant tissue. In time it may become fixed and then begin to change color to violet, purplish-red, or bluish-tinged, and finally, though rarely, ulceration may occur. Unless the nodules become ulcerated they do not give rise to pain and are not tender to the touch. Associated inflammatory reaction seldom occurs.[5]

The deposition of cutaneous nodules is usually about the ventral surface of the

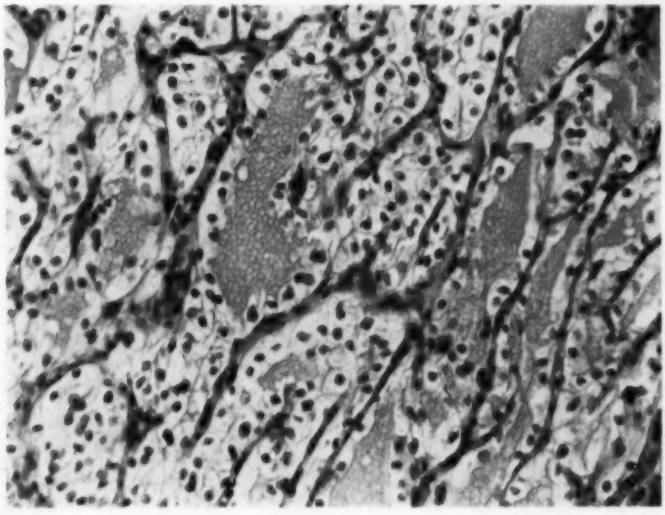


Fig. 13 (Case 2).—High-power view of the metastatic lesion, showing the pattern of clear cells which repeats itself with monotonous regularity. The nuclei are small and arranged against the basement membrane. The tubules are supported by a delicate reticulum of fibrous connective tissue. The nuclei do not show the expected characteristics of malignancy. Reduced slightly from mag. × 260.

chest and abdomen.[2,5] The head is frequently involved. The sporadic appearance of cutaneous metastases, singly or in large numbers up to 20 or more, confirms the hematogenous route of spread, without doubt.[3] This route of spread suggests a plausible explanation for the frequent occurrence of metastases about the face and head. It does not explain how widely disseminated lesions can manifest themselves and leave the lungs unaffected. These cutaneous deposits are amenable to surgery, and their true nature may thus be determined.

Summary

Two cases of renal carcinoma metastatic to the orbit are presented. In each instance the secondary lesion appeared at a long interval after the presumed eradication of the primary tumor. In the first case carcinoma was found in the remaining kidney at autopsy. This was either a primary lesion or represented a seeding from the original tumor, and it may have been the origin of the secondary lesion in the sinus. The finding of inactive foci in the lungs, as reported elsewhere,[4] suggests that the same condition may exist with respect to deposits in the skin.

The unpredictable natural history of this tumor permits optimism in the treatment of both the primary and the metastatic lesions.

655 Sutter St. (2).

REFERENCES

1. Biendara, E.: The Clinical Manifestation of Metastatic Hypernephroma in the Nose and Sinuses, Ztschr. Laryng. Rhin. Otol. 30:313, 1951.

2. Chance, B.: A Case of Secondary Hypernephroma of the Iris and Ciliary Body, J. A. M. A. 48:475, 1907.

3. McNattin, R., and Dean, A.: A Case of Renal Adenocarcinoma with Unusual Manifestation, Am. J. Cancer 15:1570, 1931.

4. Saphir, O.: The Fate of Carcinoma Emboli in the Lung, Am. J. Path. 23:245, 1947.

5. Scorer, C. G.: Cutaneous Metastases from Renal Neoplasm, Brit. J. Urol. 23:250, 1951.

6. Throckmorton, M. A.: Prognosis in Hypernephroma, J. Urol. 73:773, 1953.

7. Willis, R. A.: Pathology of Tumors, St. Louis, The C. V. Mosby Company, 1953.

On the Accommodative Convergence and the Proximal Convergence

KENNETH N. OGLE, Ph.D., and THEODORE G. MARTENS, M.D., Rochester, Minn.

The roles played by the accommodation-convergence synkinesis and by the proximal influences in the total convergence of the eyes required for a given viewing distance may be factors to be considered clinically. They may be important in the prescribing of refractive corrections, in the understanding of asthenopic symptoms from heterophorias, and in the more general problem of accommodative strabismus.

Asher [1] expressed the belief that the subject's conscious estimate of the position of an object plays as important a role as does the accommodative convergence. Furthermore, he found evidence that the proximal factor predominates in patients with asthenopia and also affects the results obtained in accommodative squint with positive lenses. In a similar vein, Guzzinati [2] found that the proximity factor affects and often determines convergence and, particularly, is reduced nearly one-half in persons showing a convergence insufficiency.

The two common methods for estimating the change in convergence due to a change in the stimulus to accommodation utilize phoria measurements, while stimulation to fusional convergence is prevented. In Figure 1, the diagram on the left illustrates, for a subject who is esophoric, the fusion-free convergence of the eyes for a distant object indicated by Δ_θ prism diopters (Δ_θ taken positive when the fusion-free convergence relative to the fixation point is esophoric, negative when it is exophoric). The angle Δ_θ is the actual angle of convergence under these conditions for a distant object.

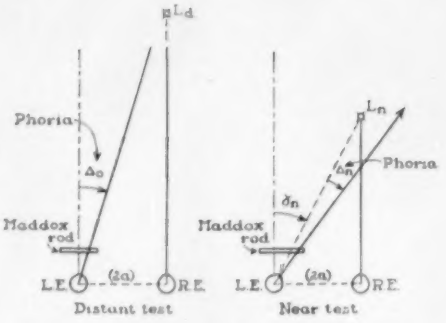


Fig. 1.—Diagrams showing geometric relationships of the visual axes of the eyes with esophoria at distant and near vision.

In the right-hand diagram, the object of regard, the stimulus to accommodation, is at a near visual distance. The convergence that would be demanded if both eyes were to fixate the object would be the angle γ_n. This angle, in prism diopters, would be equal to the interocular separation ($2a$), in centimeters, multiplied by the dioptric value (meter angle) of the distance of the object from the eyes. When fusion is prevented by a Maddox rod, only one eye can respond to the stimulus to accommodation as provided by the object at the near distance (D diopters). Suppose the lateral phoria for this near distance is measured to be Δ_n prism diopters, again in the direction of an esophoria. Then the eyes are actually pointing in an overconverged position from the one normally demanded by the near object, if both eyes were used.

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Mayo Clinic and Mayo Foundation; Section of Biophysics and Biophysical Research (Dr. Ogle) and Section of Ophthalmology (Dr. Martens). The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

The actual change in the fusion-free convergence which would result from the change in the stimulus distance of the test object from distant to near vision would be $\gamma_n+\Delta_n-\Delta_0$. The change in this convergence for each diopter of increased nearness of the test object would be

$$R_d=(\gamma_n+\Delta_n-\Delta_o)D=(2a)+(\Delta_n-\Delta_o)/D \quad (1)$$

Suppose, for example, that at distant vision (considered infinite) the phoria is $\Delta_0=+2^\Delta$ (esophoria) and that, at a near distance of, say, 50 cm. ($D=2$ diopters), the phoria is $\Delta_n=-4^\Delta$ (exophoria). If the interocular separation ($2a$) is 6.4 cm., then the change in convergence due to change in nearness of the test object would be

$$R_d=6.4+(-4-2)/2=6.4-3=3.4^\Delta/\text{D}.$$

The second usual method for estimating the change in convergence due to a change in the stimulus to accommodation involves, first, the measure of the lateral phoria at a near visual distance, Δ_n prism diopters. Then, ophthalmic spheres of dioptric power D diopters are placed before the eyes to change the stimulus to accommodation, and the phoria, Δ_n' prism diopters, is now measured. The ratio of the change of phoria caused by the change in stimulus to accommodation of 1 D. would be

$$R_c=(\Delta_n'-\Delta_n)/D \quad (2)$$

For example, suppose that the normal near phoria is measured to be $\Delta_n=-4^\Delta$ (exophoria), and with -2.00 D. lenses before the eyes, which increase $(+)$ the stimulus to accommodation, the near phoria now measures $\Delta_n=+1^\Delta$ (esophoria); then the change per diopter would be

$$R_c=(1+4)/2=2.5^\Delta/D.$$

Now the computed values for R_d and R_c, obtained from phorias carefully determined by these two methods, are not commonly the same. Generally the ratio, R_d, found when the test object is moved from distant to a near observation distance, is larger than that, R_c, found when the test object is at a fixed near distance and lenses are used to change the stimulus to accommodation. Actual change in the stimulus to accommodation in the two methods may be identical. One is forced to assume, therefore, that something has been added to the pure accommodative convergence effect, when the test object is moved from distant to the near observation distance, that is not present when the observation distance is kept constant. The difference in the two ratios is, therefore, attributed to a convergence initiated by the psychic "awareness of distance"—and this factor is usually called a "proximal" convergence. It is clear, therefore, that only the second method, in which the change in convergence is measured at a fixed observation distance with a change in stimulus to accommodation produced by spheres, gives the true accommodative convergence-accommodation, the (A-C)/A, ratio. The denominator of this fraction actually indicates the change in the stimulus to accommodation.

Ittelson and Ames [3] presented data indicating that the accommodation tended to change with the apparent distance of familiar objects, even as influenced by a change in their angular size, though the actual distance remained the same. The authors concluded also that there was change in convergence, but this change was held [4] to be due to the accompanying accommodative convergence. However, Hofstetter [5] independently presented data which did suggest that a convergence change as well as an accommodative influence might arise from the sense of proximity alone. Thus there is precedent for the use of the term "proximal factors" for the factors to which the difference between the ratios obtained by the two methods can be attributed.

In any ocular measurements such as those of phoria, the variability of the phorias must be taken into account as well as the instrumental precision in the actual measurements. The computed values of the accommodative convergence and of the proximal convergence obtained will accordingly be affected. This variability may pertain to long-term changes, on the basis of a fundamental stability of the associations [and, so far as the (A-C)/A ratio is concerned, there is evidence for such a stability [6]], or to those moment-to-moment

changes which seem to occur in all physiological processes. In this instance it may very well depend also on ocular motor stresses just preceding the test as well as on the completeness of the psycho-optical reflexes associated with fixation and with attention. Single phoria measurements, then, may not yield representative results, and it is desirable for accuracy to have a series of measurements over rather wide ranges, for then the individual variations may be ironed out or their effect may be reduced through the smoothing process of fitting a curve to the data.

The distributions both of the accommodative convergence-accommodation ratio [(A-C)/A] and more especially of the proximal convergence-distance ratio [(P-C)/A] have not been adequately presented in the literature. The purpose of this paper is to describe data bearing on this problem, obtained (1) by the two phoria methods just described and (2) by the method of fixation disparity.

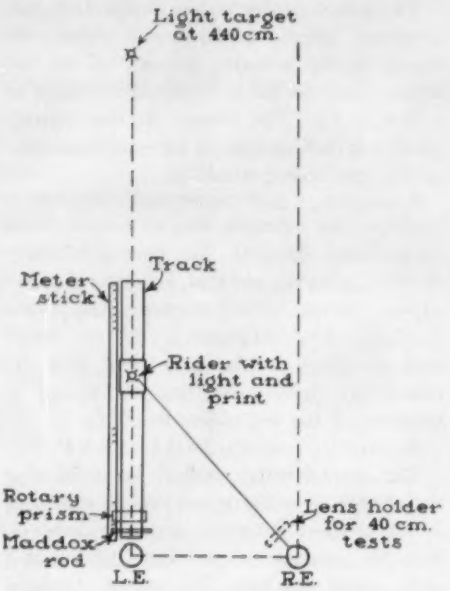

Fig. 2.—Scheme of apparatus used for making lateral phoria measurements at different observation distances.

Heterophoria Methods

The lateral phorias were measured with a Maddox rod before the left eye in an experimental arrangement illustrated in Figure 2. The subject's head was held by a suitable headrest and chin-cup. Directly in front of the left eye, at a distance of 440 cm. (0.22 D.), a small 3-volt lamp was attached to a wall in contact with a printed chart. This lamp served as the "muscle" light for distant vision. In line with this lamp and the left eye was set up a cast-iron optical bench. On this a rider, which supported a small cystoscope lamp, could be placed at any distance from 1 meter to 14 cm. before the left eye. Mounted directly behind the cystoscope lamp and in contact with it was a small card of print which was used to increase the stimulus to accommodation.

Mounted directly before the left eye was a Maddox rod. Thus the left eye would always see a vertical streak of light. Mounted in front of the Maddox rod was a calibrated rotary prism. The right eye was free so far as possible from any instrumental parts in its fixation of the test chart and light. For the distant-vision measurements the rider was removed from the optical bench. For the tests with the cystoscope light kept at the near observation distance of 40 cm., an ophthalmic lens holder could be mounted and centered before the right eye. The end of the meter stick, attached to the track, by which the position of the rider could be adjusted for a desired observation distance, could be brought directly below the pole of the cornea of the left eye by means of a suitable sighting device. Thus, the distance of the target could be accurately located before the eyes.

The measurements were made by an assistant, who adjusted the rotary prism. During a given test the left eye was occluded most of the time and only momentarily allowed to see the Maddox streak. Following this short exposure, of about one-half second, the subject reported

whether the streak appeared to the right or left or centered with the light. The phoria was measured by a method of limits, that is, the prismatic deviations within which the subject reported that the Maddox streak appeared to coincide with the light. The average prismatic deviation was determined from three separate measurements. The prismatic deviation was read from the rotary prism to within 0.5Δ.

The fusion-free position of the eyes, the phoria, was measured, first, when the observation distance was changed in (diopter) steps from 440 cm. (0.22 D.) to a maximum of 14 cm. (7.0 D.). Second, the phorias were determined with the "muscle" light set for 40 cm. for a sequence of plus and minus ophthalmic spheres of increasing power, in 0.5 D. steps, until either the subject complained of excessive blurring of the image or the measurements became erratic.

Twenty-eight subjects, mostly in the age range of 19 to 39 years, were used for this part of the study. Only one subject was older than 39 years. For the most part these subjects were laboratory technicians; a few were young resident physicians. The majority had normal vision without correction, and no subject was tested while wearing spectacles. The interocular separation was measured for each subject by means of a millimeter rule, which was sufficiently accurate for this study.

Certain corrections have to be made in the data obtained. In the first place, the true prismatic deviation caused by the rotary prism is less than that indicated, when used for near observation distances. This correction can be determined from the well-known formula that the true prismatic deviation, Δ_a, is equal to the deviation indicated on the scale, Δ_s, divided by the quantity $(1-h/p)$, in which h is the distance of the prism from the center of rotation of the eye and p is the observation distance measured from the same point. The calculations for

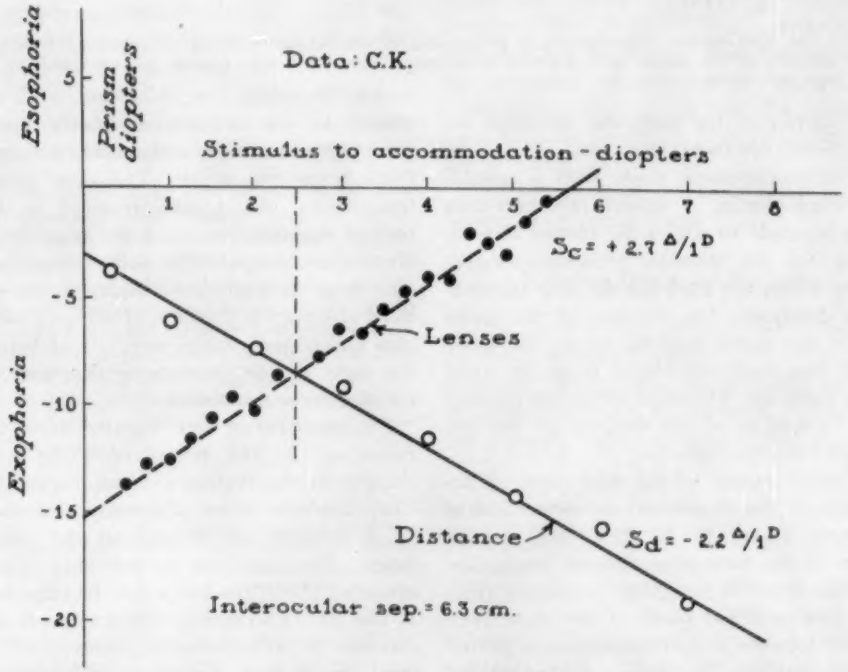

Fig. 3.—Graphic representation of phoria data of one subject, showing the typical linear relationship between phoria and stimulus to accommodation.

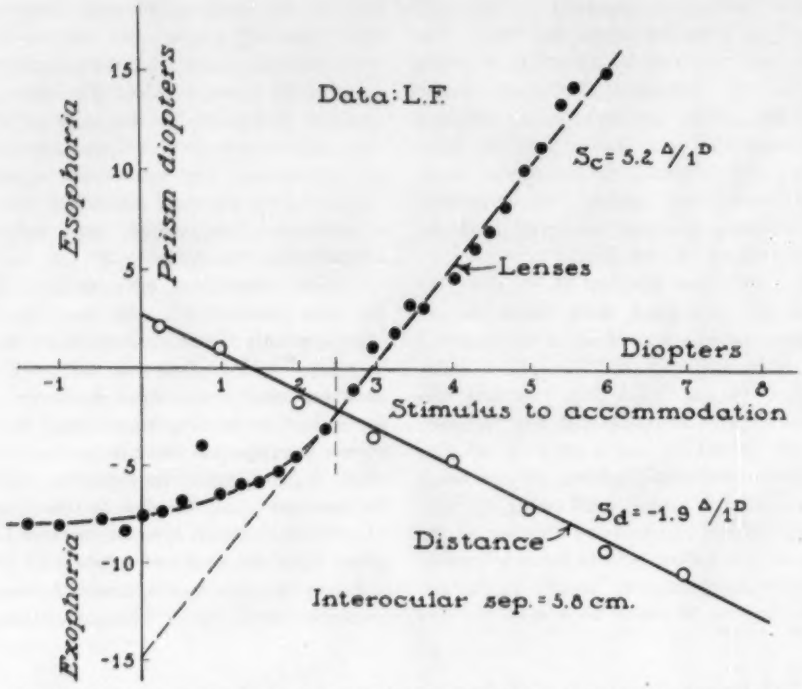

Fig. 4.—Graphic representation of phoria data of one subject, showing the departure from linearity of the phoria with stimulus to accommodation when plus spheres are used with a near test distance.

the correction for prismatic deviation for all object distances were also checked by actual measurement made with a suitable telescopic device. A second correction must also be made to obtain the correct dioptric value for the stimulus to accommodation when lenses are used for the near observation distances. The distance of the image of the test object from the eye for the lenses used was easily calculated from the usual lens formulas. The third correction involves the calculation of the distance of the test target from the right eye.

Typical results of the two types of response of the 28 subjects are illustrated in Figures 3 and 4. In these, the dioptric value of the observation distance (reciprocal of that distance measured in meters from the first principal plane of the right eye) or the stimulus to accommodation is plotted as the abscissa. The corrected Maddox-rod prismatic deviation, in prism diopters, is plotted as the ordinate—esophoria (positive) above the origin and exophoria (negative) below the origin. The open circles indicate the phoria measurements in that part of the study in which the observation distance is changed. The solid circles indicate those measurements, obtained for the fixed observation distance of 40 cm., when plus and minus spheres were placed before the right eye to increase or decrease the stimulus to accommodation.

An inspection of these Figures shows the following: 1. The phoria occurring with changes in observation distance (open circles) appears to be adequately described by a straight line throughout the whole range. The variations in individual measurements about this line are to be expected. 2. The phoria occurring with changes in the stimulus to accommodation (lenses) for a fixed observation distance (solid circles) tends also to follow a linear relationship.

For about one-half of the subjects, however, the phorias measured departed from this linearity when the plus lenses of increasing power were used (in the direction of decrease in stimulus to accommodation). Instead, the phorias leveled off, as the example in Figure 4 shows. For the subjects whose curves were of this latter type, the eyes increasingly fail to respond to the change in stimulus produced by plus lenses with a fixed object at near. These data, therefore, would suggest that, in determining the accommodative convergence-accommodation ratio, minus spheres, to increase the stimulus to accommodation, on the whole will yield more reliable results than plus spheres.

The slope of the line that describes a given set of data corresponds to the change in phoria produced by a change of 1 D. stimulus to accommodation. For the constant observation distance, with the change in the stimulus to accommodation produced by the power lenses, this slope, S_o, is equivalent to the pure* accommodative convergence-accommodation ratio [R_o=(A-C)/A]. For the data of the two subjects illustrated in Figures 3 and 4, the (A-C)/A ratios are 2.7△ and 5.2△ per diopter of change in stimulus to accommodation, respectively. Alpern [7] has already shown that the (A-C)/A ratio determined in this manner is independent of testing distance.

The slope, S_d, that describes the phoria with change in observation distance (for the two subjects, −2.2△ and −1.9△ per diopter of change in observation distance, respectively) involves the sum of both the accommodative convergence [(A-C)/A ratio] and the proximal convergence [P-C)/A ratio]. For shorthand purposes, let u=the proximal convergence-distance ratio; v=the accommodative convergence-accommodation ratio; S_d=the slope of the phoria-distance data line (open circles), and S_o=the slope of the phoria-stimulus to accommodation data line (solid circles). Then, from Equations (1) and (2) above

$$R_d = u + v = (2a) + S_d$$

$$R_o = v = S_o$$

whence the proximal convergence factor would be

$$u = (2a) + S_d - S_o \qquad (3)$$

For the two subjects illustrated in Figures 3 and 4, the proximal convergence factor, u, would be $u = 6.3 - 2.2 - 2.7 = 1.4^{\Delta}/D.$ and $u = 5.8 - 1.9 - 5.2 = -1.3^{\Delta}/D.$, respectively. The fact that for one of these two subjects the proximal convergence is negative is noteworthy. Four (14%) of the twenty-eight subjects showed a negative value for the proximal convergence.

The summary of the results for the 28 subjects is given in Table 1.

Fixation-Disparity Method

This method rests on the fact that if a muscular imbalance exists, even in normal binocular observation, the eyes will fail to converge accurately at the point of fixation by a small angle, overconverging in eso-

* The change in apparent distance of the fixed test target in the near vision tests described earlier in this paper, which might be associated with the magnification of the retinal image caused by the plus and minus ophthalmic spheres, by virtue of the size constancy phenomenon, would hardly introduce a proximal factor in those near measurements. The magnification would be of the order of 1.5% to 2.0% per diopter power, which correspondingly would introduce a change in apparent distance of only about 0.05 D. per diopter of lens power.

TABLE 1.—*Results of the Phoria Tests to Determine the Accommodative Convergence and Proximal Convergence (Twenty-Eight Subjects)*

	Accommodative Convergence-Accommodation (v)	Proximal Convergence-Accommodation (u)	Interocular Distance ($2a$)	Sum ($u+v$)	Age, Yr.
Mean	3.6 △/D	0.9△/D	6.4 cm.	4.4 △/D	27
Standard deviation	1.25△/D	0.9△/D	0.31 cm.	1.17△/D	2.6
Range	1.8 to 7.4	−1.2 to 2.9	5.7 to 7.2	2.3 to 7.7	19 to 50

phoria, underconverging in exophoria.[8,9] This angular error in convergence, which is very small and can be measured only in minutes of arc, is called the "fixation disparity." Its existence means that the images of the fixation point and of all other points in the frontoparallel plane are transversely disparate: These images from the two eyes cortically have "slipped" within the limits set by Panum's areas of fusion. The magnitude of the disparity depends on the amount of detail in the pattern observed, the magnitude of the heterophoria, and the prism vergence limits. There are also individual variations, probably depending on the strength of the compulsion for fusion reflex and smoothness of general binocular coordination. More detailed description of the instrumentation and treatment of data to determine the accommodative convergence-accommodation ratio may be found elsewhere.[10,11]

The fixation disparity is determined for distant vision (2.5 meters) and for near vision (33 cm.) when accommodation and convergence are disassociated by forcing a change in the convergence with prisms base-in and base-out. At near vision, in addition to the prisms, this disassociation is forced by introducing ophthalmic spheres before the eyes. Typical data are illustrated by the graphs in Figures 5*A* and *B* and 6*A* and *B*. From the two sets of data obtained at the near observation distance (prisms and lenses), a quantitative relationship for the accommodation and convergence association can be derived (Figs. 5*C* and 6*C*).

The slope of the derived line is the accommodative convergence-accommodation ratio $[S_c=(A\text{-}C)/A]$ in prism diopters

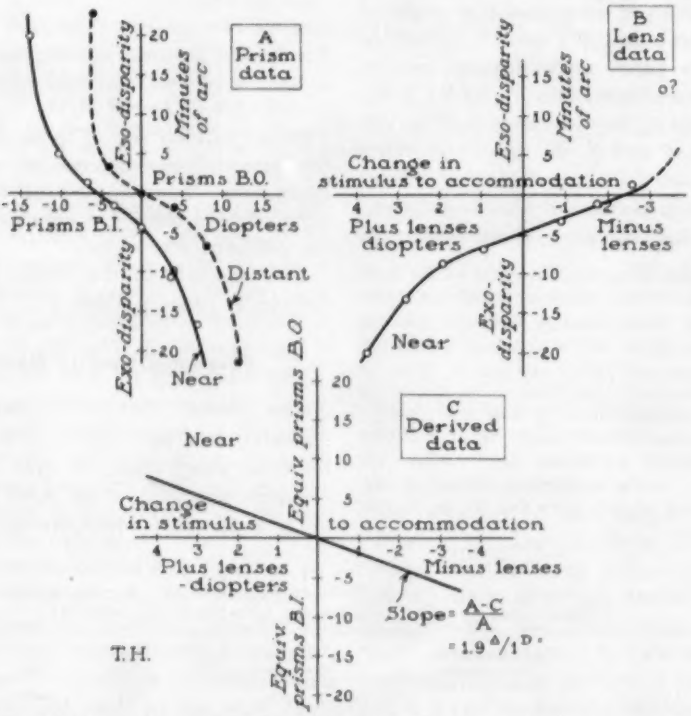

Fig. 5.—Typical graphic representation of fixation-disparity data for distant and near vision. *A*, curve for disassociated accommodation and convergence by prisms. *B*, curve for the disassociation produced by power lenses. *C*, derived data showing relationship between the equivalent prismatic deviation and stimulus to accommodation.

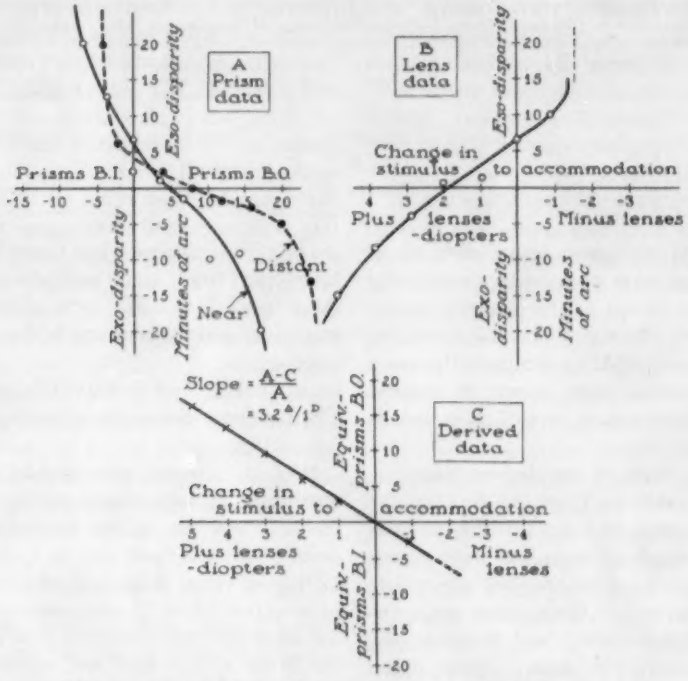

Fig. 6.—Same as in Figure 5, for another type of subject.

per diopter change in the stimulus to accommodation over the range of response. The following discussion should make clear that the ratio of the change in prism vergence that produces the same disparity (ocular motor imbalance) as does a given change in stimulus to accommodation is the same as that ratio [the (A-C)/A ratio] determined by phoria methods. Suppose a given subject is orthophoric for a given observation distance. If, now, 1 D. minus ophthalmic spheres are placed before the eyes, the stimulus to accommodation is increased. Through the accommodation or convergence synkinesis there is an accompanying innervation for a convergence, and an ocular motor imbalance exists when fusion is maintained. If fusion is interrupted by occluding one eye (by a Maddox rod, say), an esophoria will be measured, say, 3.5Δ. The eyes will be actually overconverged by 3.5Δ, and we say that this phoria is the measure of the imbalance to be overcome when fusion is obtained. That is, a divergent fusional movement of 3.5Δ must occur when fusion is regained on removing the Maddox rod. The ratio of 3.5/1Δ per diopter is the (A-C)/A ratio. Thus, if we then remove the minus lenses, we can introduce the same ocular motor imbalance by forcing the same divergent fusional movement as a result of putting 3.5Δ base-in prisms before the eyes. The fixation-disparity technique provides a method of determining what forced prismatic deviation will produce the same change in motor imbalance as does a given change in stimulus to accommodation. Hence we would find that a forced prism divergence (3.5Δ) would produce the same esodisparity as did the −1 spheres before the eyes. Thus the (A-C)/A ratio would be 3.5/1Δ per diopter of change in stimulus to accommodation.

The fixation-disparity technique has the advantage over the phoria methods in that

TABLE 2.—*Summary of Results for the Accommodative Convergence and Proximal Convergence Obtained from Fixation-Disparity Measurements (104 Subjects)*

	Sum ($u+v$)	Accommodative Convergence-Accommodation (v)	Proximal Convergence-Accommodation (u)
Mean	4.91△/*D*	3.39△/*D*	1.52△/*D*
Standard deviation	1.85△/*D*	1.19△/*D*	1.62△/*D*
Range	1.0 to 11.0	1.0 to 7.0	−3.0 to +6.0

each eye has the same visual task at all times and the same stimulus to accommodation and that fusion of the images is maintained. From the series of data points the smoothed curve tends to eliminate the small erratic variations that occur in natural binocular coordination, as well as errors of measurement.

Now, the slope of the derived data line (Figs. 5*C* and 6*C*) gives directly the (A-C)/A ratio—the v used in the previous section. From the distant and near prism-fixation disparity data one can interpolate on the curves to find those prism vergences for which the disparity, and therefore the motor imbalance, is zero. These prism vergences would correspond to the fusion-free position of the eyes—the equivalent phoria measured from the convergence demanded by the test targets. Thus, if Δ_0 is the equivalent phoria for distant vision and Δ_n is that for near, the slope S_d, which is the sum of the accommodative convergence and the proximal convergence per each diopter change in observation distance, would be found from Equation (1). One can then find the proximal factor by subtracting the (A-C)/A ratio, found from the slope S_c of the line that describes the derived data.

For the subject whose data are graphed in Figure 5, $\Delta_0=0.0^\Delta$; $\Delta_n=-5.5^\Delta$ (exophoria); interocular distance $(2a)=6.3$ cm., and thus the (A-C)/A ratio$=v=1.9^\Delta/D$. The sum of the accommodative convergence and the proximal convergence, $u+v,=6.3+(-5.5-0)/(3.0-0.25)=4.3^\Delta/D$. The proximal convergence factor, $u,=4.3-1.9=2.4^\Delta/D$.

For the subject whose data are graphed in Figure 6, $\Delta_0=+8^\Delta$ (esophoria); $\Delta_n=+5^\Delta$ (esophoria); interocular distance $(2a)=6.4$ cm., and the (A-C)/A ratio$=v=3.2^\Delta/D$. The sum of the accommodative convergence and the proximal convergence, $u+v,=6.4+(5-8)/(3.0-0.25)=5.3^\Delta$/D. The proximal convergence factor, $u,=5.3-3.2=2.1^\Delta/D$.

With use of the experimental setup for obtaining the fixation-disparity measurements, where the subject looks through the usual phorometer and sees an approximately 12-degree visual field, 104 subjects ranging in age from 14 to 72 years were tested. For the most part these subjects were patients at the Mayo Clinic who had registered with the Section of Ophthalmology. Therefore they may not be entirely representative of

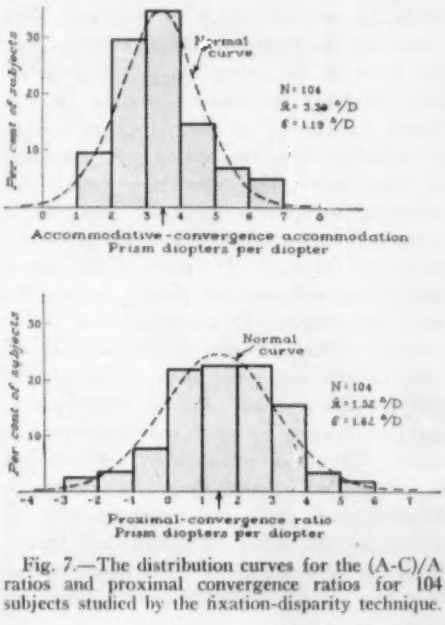

Fig. 7.—The distribution curves for the (A-C)/A ratios and proximal convergence ratios for 104 subjects studied by the fixation-disparity technique.

the general population. The method just outlined was used to determine the accommodative convergence and the proximal convergence factors on all 104 subjects. The results are summarized in Table 2.

The statistical distributions of the results are illustrated in Figure 7. From the calculated values of the mean and of the standard deviation, normal curves were computed, and these are shown superimposed on the block distribution diagram. The (A-C)/A distribution is generally believed not to be a normal one. In this study no ratios were found less than $1.0^{\Delta}/D$. The distribution of the proximal convergence ratios appears for practical purposes to be fairly normal about the mean of 1.52Δ per diopter change in visual distance. The range of the proximal convergence ratios is greater than that of the (A-C)/A ratios.

Comment

The mean (A-C)/A ratios obtained by the two tests and the two groups of subjects are very nearly the same, and their standard deviations are practically identical. The mean also is similar to that which has been reported in the literature, although the direct comparison of results is difficult because of the differences in the methods of measurement and because in most studies correction factors frequently have not been applied. There are reasons for believing that the accommodation-convergence relationship, as quantitatively expressed in the (A-C)/A ratio, is a fairly stable association. We do not have data showing long-term trends in the association.[6] Certainly there are day-to-day variations, probably about a fairly stable mean. It appears not to be easily susceptible to alteration by orthoptic training. Cycloplegic drugs do dramatically increase the ratio,[11] but myotic drugs appear to have little influence.[12]

In this study the difference is to be noted between the means and their standard deviations for the proximal convergence factor (u) obtained by the Maddox rod phoria test (0.9, $\sigma=0.9$) and by the fixation-disparity method (1.52, $\sigma=1.62$). It is difficult to know how significant is this difference. The standard error in both sets of measurements is about the same, namely, 0.18. The difference ($0.62^{\Delta}/D$) is barely greater than twice the standard error of the combined groups (± 0.24), which by some is the criterion of significance. Even at that, the difference is little more than 0.5Δ. For a reading distance of 33 cm. the difference between the two results corresponds to about 1.75Δ, which certainly would be measurable.

Granting that this difference is clinically significant, how can we account for it, and what is its meaning with regard to the proximal convergence factor? To be considered are the differences in the experimental situations under which the data were obtained. These differences can be best seen from Table 3.

Because the (A-C)/A ratios found are so nearly the same, it is possible that the difference in the number of subjects and the difference in population groups do not

TABLE 3.—*Comparative Statistics from the Heterophoria and Fixation-Disparity Tests in the Measurement of the (A-C)/A and (P-C)/A Ratios*

	Maddox Rod Technique	Fixation-Disparity Procedure
(A-C)/A ratio (σ), Δ/D	3.6, S.D.=1.25	3.39, S.D.=1.19
Proximal factor (u), Δ/D	0.9, S.D.=0.9	1.52, S.D.=1.62
Population	Nonpatients	Mostly patients
Age, yr.	27, S.D.=2.6	31, S.D.=12.8
Subjects, No.	28	104
Visual circumstances	One eye Small field Only lens holder	Both eyes—fusion Approx. 12-degree field Phorometer

account for the difference in the proximal convergence ratios. It is possible that the difference in the age ranges of subjects in the two groups could be an important factor and, as such, would indicate a decrease in the exophoria in near vision with increase in age. However, the literature tends to show little or no correlation between the heterophoria measured and age.

A difference in the proximal convergence ratios could perhaps result from the different visual conditions under which the two tests were made. Uniocular vision was used in the first; binocular vision with fused images, in the second. The larger field in the second might enhance the stimulus for a psychic awareness of distance. It would seem, however, that any influence the phorometer close to the eyes might have on this awareness would be constant for both distant and near observation distances. However, one must seriously consider whether the differences between these factors are actually significant.

Difficult to understand is the fact that negative values of the "proximal" convergence ratios are found, if this is a measurement of convergence initiated by awareness of nearness.[18] In our fixation-disparity measurements negative values are found for about 16% of the 104 subjects tested. The existence of a negative proximal convergence factor means that this "sense" actually decreases the convergence initiated by the accommodative convergence. If this factor is a true psychic "awareness of distance," one must conclude that for some subjects this "awareness" is insufficient.

On the assumption that there is no significant difference between the values of the proximal convergence measured in the foregoing two tests, one would have to take the results from the larger population as representing the more probable values. On the average, this would correspond to 1.5Δ for each diopter that the visual object is brought nearer the eyes. From this method of measurement, therefore, the proximal convergence is less than one-half the accommodative convergence. From distant vision to a near vision of 40 cm. the proximal convergence would be 3.75Δ. Before we can be sure that this factor represents a constant part of the total convergence pattern of each person, more data are needed to find (1) the variation with repeated tests; (2) variation with greatly different instrumentation, that is, test targets; (3) variation with age. (Our data have not suggested any significant variation with age.)

While the linear relationship between the accommodative convergence and the stimulus to accommodation is clearly emphasized by the fixation-disparity data, the data obtained by the phoria measurements emphasize also a linear relationship between the proximal convergence and change in the stimulus to accommodation. The sum of the accommodative convergence and the proximal convergence ($u+v$) shows the extent to which these two functions contribute to the convergence demanded at a given observation distance. (The fusional convergence will make up the difference.) The mean value of ($u+v$) for our population is $4.9^{\Delta}/D$, with a standard deviation of $1.8^{\Delta}/D$, and the mean interpupillary distance is 6.3 cm. Hence, in changing fixation from a distant object to one at the near distance of 40 cm. there would be on the average an exophoria of $(6.3-4.9)\times 2.5 = 3.5\Delta$. This is in agreement with the usually accepted figure that there is a normal physiologic exophoria at near of about 4Δ.

It is of interest to see what relationships may be suggested from a statistical study of the data obtained from the selected population used in this study. Probably 104 subjects is not a large enough number to warrant definitive conclusions to be drawn, however.

1. *Myopia and Hyperopia.*—There were 15 subjects among the 104 whose refractive error was unquestionably myopic, and there were 21 whose error was unquestionably hyperopic. There were undoubtedly many more subjects who might have been included in these groups, but too often the astigmatic corrections made a decision uncertain.

No significant correlation of the degree of myopia and hyperopia with the magnitude of the (A-C)/A ratio or the proximal convergence [(P-C)/A] ratio was evident. However, when the myopes and the hyperopes were separated each into two groups according to whether the (A-C)/A ratio was greater or less than the mean value of 3.4$^{\Delta}$/*D* of the entire 104 subjects, it was found that only 2 of the 15 myopes had an (A-C)/A ratio less than 3.4$^{\Delta}$/*D*. That is to say, the great majority of myopes have a higher (A-C)/A ratio than the average. There was a tendency also for hyperopes to have a somewhat lower (A-C)/A ratio than the average, but less strikingly so. This relationship of a higher (A-C)/A ratio with myopia has previously been suggested, in the study of Manas.[14] A significance test shows that for our data the association of the higher (A-C)/A ratio with myopia, and of the lower ratio with hyperopia, is significant at the 1% level. This association suggests that the innervation for a given change in accommodation in myopes must be greater than that for the normal.

There appeared to be no significant relationship between myopia or hyperopia and the (P-C)/A, proximal convergence, ratio.

2. *Greater Exophoria at Near.*—We can select those subjects whose exophoria at distance was less than 4Δ and at the same time whose exophoria at near (33 cm.) was greater than 6Δ, a phoria pattern which might, according to the Duane classification, be called "convergence insufficiency." There were 18 subjects among the 104 whose oculomotor imbalance fell in this range. Their corresponding (A-C)/A ratios and proximal convergence ratios were then compared to those of the remaining subjects. There were 14 of these 18 who had (A-C)/A ratios less than the average of the 104. However, 16 of the 18 had proximal convergence ratios less than 1.5$^{\Delta}$/*D*. The comparison shows statistically that both the (A-C)/A ratio and the (P-C)/A ratio of the group of subjects who had convergence insufficiency are significantly less than those of the remaining subjects, at the 3% and 0.03% levels, respectively. This result is similar to that reported by Guzzinati.[3]

3. *Esophoria at Near.*—Again following Duane's classification for convergence excess, we selected those subjects who were more esophoric at near than at distance. Subjects requiring an additional correction for near were excluded. There were 24 subjects in this group. A study showed a significant association at the 1% level in that this group tended to have a higher (A-C)/A ratio than the other subjects. While there was also a tendency for the proximal convergence to be larger than that of the group as a whole, the association was less statistically significant.

It was found by statistical comparison that there was an increased (A-C)/A ratio in this group over that of the remaining subjects significant at the 0.4% level. However, there did not seem to be at the same time a significant decrease in the proximal convergence.

Thus it would seem that both the accommodative convergence and the proximal convergence were reduced in convergence insufficiency but that only the accommodative convergence increased in convergence excess.

The clinical value of such information about oculomotor coordination may be important in such cases as the following:

Case 1.—A 33-year-old physician complained of difficulty in studying and of general asthenopia associated with the near use of the eyes. He had a refractive error of R. E. $-2.00-0.50\times 13$; L. E. $-2.00-0.25\times 156$ and a convergence excess at near. A complete test using the fixation-disparity technique showed an equivalent phoria: distant vision = 1.5$^{\Delta}$ esophoria; near vision = 10.0$^{\Delta}$ esophoria. The accommodative convergence-accommodation ratio, (A-C)/A, was found to be 5.1$^{\Delta}$/*D*, which is higher than normal, and the proximal convergence factor was found to be 4.1$^{\Delta}$/*D*. In this case the convergence excess of this patient is due to an accommodational factor as well as to a proximal convergence factor, since both quantities are greater than normal. The

sum of the two factors is $9.2^{\Delta}/D$ for a demand convergence of $6.3^{\Delta}/D$. To some extent there may have been functional factors in the patient's complaints.

CASE 2.—A 54-year-old man complained of visual fatigue, tendency toward diplopia, and discomfort in reading. The refractive error was R. E. $-0.25-0.50\times180$; L. E. $-0.50-0.25\times180$. A large exophoria at near was found with an addition of +2.50 D. The fixation-disparity technique was used for a complete work-up of oculomotor pattern. Equivalent phorias: distant vision $=1.5^{\Delta}$ exophoria; near vision, with an add of +2.50 D. both eyes, $=15^{\Delta}$ exophoria. The accommodative convergence-accommodation ratio, (A-C)/A, was found to be $5.2^{\Delta}/D$, and the proximal convergence factor was essentially zero. Because the +2.50 D. spheres were used for near vision, the stimulus to the accommodation was essentially the same for both the distant and the near test. Consequently, there would be no accommodative-convergence change between tests. With the proximal convergence so low, the convergent positions of the two eyes at which there would be no muscular imbalance would be the same at both the distant and the near test. Measured from the distant test plane, the phoria would be relatively small; measured from the near test plane, there would be a large exophoria of approximately 15Δ to 18Δ. The difference in the measured phorias would be independent of the (A-C)/A ratio. Thus, when a full additive correction for vision on near objects is required, as in presbyopia, only the proximal convergence factor can reduce the exophoria otherwise to be expected.

Summary

The accommodative convergence-accommodation ratios and the proximal convergence ratios were determined, first, for 28 subjects by the phoria technique, using a series of measurements to reduce effects of variation, and, second, for 104 subjects, for the most part clinical patients, using the fixation-disparity technique, which was believed to give more stable data, since the test requires fusion and both eyes are subject to the same stimulus to accommodation. The data suggest that if the accommodative convergence is to be determined by measuring the phoria at near visual distance with only a few measurements, minus lenses would probably lead to less error than plus lenses.

The (A-C)/A ratios were essentially the same from the two methods, the mean being $3.5^{\Delta}/D$, with a standard deviation of $1.2^{\Delta}/D$. The mean proximal convergence ratio was different, being $0.9^{\Delta}/D$ (S. D.$=0.9^{\Delta}/D$) from the phoria technique and $1.5^{\Delta}/D$ (S. D.$=1.62^{\Delta}/D$) from the fixation-disparity technique. The distribution of the proximal convergence ratios for the 104 subjects seemed to be normal, and 16% of the ratios were negative.

The association of the proximal convergence with dioptric change in the distance of the test object was shown to be linear, as was also that of the accommodative convergence with change in the stimulus to accommodation. To what extent the difference between the proximal convergence ratios measured by the two methods is significant is not clear, but the difference in selection of the two groups of subjects and in the conditions of the tests is emphasized. More weight is attached to the proximal convergence measured by the fixation-disparity technique than to that measured by the phoria technique. Statistical studies showed the following: As a group, myopes had a higher (A-C)/A ratio than hyperopes. This was interpreted to mean that the innervation necessary to cause a given change in accommodation of a myope was greater than that of a hyperope or a normal subject. Convergence excess (by the Duane classification) was associated with an increased (A-C)/A ratio but not with an increased proximal convergence. On the other hand, convergence insufficiency (again following the Duane classification) was associated both with a decreased (A-C)/A ratio and with

a decreased proximal convergence. The data of two representative cases, one of an overconvergence at near vision and the other of a large exophoria at near in a presbyope, are presented.

REFERENCES

1. Asher, H.: Stimulus to Convergence in Normal and Asthenopic Subjects, Brit. J. Ophth. 36:666-675 (Dec.) 1952.

2. Guzzinati, G. C.: Richerche sull' importanza della convergenza prossimale in soggetti ortoforici ed eteroforici, Ann. ottal. e clin. ocul. 79:475-482 (Sept.) 1953.

3. Ittelson, W. H., and Ames, A., Jr.: Acommodation, Convergence, and Their Relation to Apparent Distance, J. Psychol. 30:43-62 (July) 1950.

4. Hofstetter, H. W.: Accommodation, Convergence, and Their Relation to Apparent Distance: A Criticism, J. Psychol. 30:393-394 (Oct.) 1950.

5. Hofstetter, H. W.: The Proximal Factor in Accommodation and Convergence, Am. J. Optometry 19:67-76 (Feb.) 1942.

6. Morgan, M. W., Jr.: Relationship Between Accommodation and Convergence, A. M. A. Arch. Ophth. 47:745-759 (June) 1952.

7. Alpern, M.: Testing Distance Effect on Phoria Measurement at Various Accommodation Levels, A. M. A. Arch. Ophth. 54:906-915 (Dec.) 1955.

8. Ogle, K. N.: Fixation Disparity, Am. Orthop. J. 4:35-39 (June) 1954.

9. Ogle, K. N.: Researches in Binocular Vision, Philadelphia, W. B. Saunders Company, 1950, pp. 36-40; 69-93.

10. Ogle, K. N. and Prangen, A. de H.: Further Considerations of Fixation Disparity and Binocular Fusional Processes, Am. J. Ophth. 34:57-72 (May, Pt. 2) 1951.

11. Christoferson, K. W., and Ogle, K. N.: The Effect of Homatropine on the Accommodation-Convergence Association, A. M. A. Arch. Ophth. 55:779-791 (June) 1956.

12. Ogle, K. N., and Sabin, F. C.: The Accommodation-Convergence Association: Effects of Neosynephrine, Pilocarpine and Physostigmine, Unpublished data.*

13. Hofstetter, H. W.: The Relationship of Proximal Convergence to Fusional and Accommodative Convergence, Am. J. Optometry 28:300-308 (May) 1951.

14. Manas, L.: The Inconstancy of the ACA Ratio, Am. J. Optometry 32:304-315 (June) 1955.

Mixed Bacterial Infections in Relation to Antibiotic Activities

III. Staphylococcal-Diphtheria Infections of Guinea Pigs

SEYMOUR P. HALBERT, M.D.; CONSTANCE SONN KAZAR, B.S., and LOIS S. SWICK, B.S., New York

The role played by antibiotic-producing strains of the normal human microflora in immune mechanisms of superficial infections is still uncertain. That such strains are extremely common in the ocular flora [1-4] as well as in the intestinal tract,[5-9] skin,[10-12] nose and throat,[13,14] and oral cavity [15,16] has now been well established. The general characteristics of a number of these antibiotics have been worked out, and many seem to be of peptide nature.[2,17-19] Where studied, the extreme frequency of such strains, their antibacterial spectra, their activity in the presence of body fluids, and the rapidity with which fluctuation in concentration of such strains can occur have all argued for their potential significance. In addition, in Shigella infections [20-22] and in diphtheria infections [23] evidence has been obtained which indicates a flourishing of antibiotic producers in the local tissues during recovery from these infections.

As an experimental approach to the analysis of the significance of these antibiotic activities in vivo, mixed infections of animals have been utilized in this laboratory. In a previous study, mice were infected with mixtures of ocular staphylococci and Clostridium septicum spores by the intramuscular route.[24] It was found that a high degree of protection against lethal outcome due to "gas gangrene" was obtained when the staphylococcal component of the mixture was antibiotically active against the clostridial strain. As an extension of these studies, it was found that highly concentrated and purified antibiotic of one of these strains was very effective prophylactically in small doses in this experimental disease.[25] The present report deals with mixed diphtheria infections of guinea pigs, in which essentially the same approach was used, also with staphylococcal strains of the ocular flora. Duliscouët [23] reported earlier that guinea pigs infected with diphtheria were protected against lethal outcome when an antibiotically active strain of throat staphylococcus was injected into the inoculation site. In addition, he also demonstrated protection against fatal diphtheria when a crude, active filtrate from the Staphylococcus was injected into the diphtheria infection site. Unfortunately, he failed to give detailed information, and apparently only a single strain of Staphylococcus was used.

Materials and Methods

The ocular staphylococci were obtained from the lids and conjunctivae of patients with either normal or inflamed conjunctivae. The techniques used for obtaining the cultures and isolating the antibiotically active strains have been described previously.[26] Most of the organisms were of the Micrococcus pyogenes var. albus group. Antibiotic assays were carried out according to the methods used earlier.

Estimations of the dosage of organisms used were made by the preparation of a standard curve, relating turbidity (in a

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From the Departments of Ophthalmology and Microbiology, Columbia University, College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital, New York.

Klett-Summerson photoelectric comparator) to viable plate counts and to total bacterial cell solids. The strain of Corynebacterium diphtheriae finally chosen as most suitable for use in the infection studies was a mitis strain (H*). In preliminary tests, a number of diphtheria strains were examined both for susceptibility to the staphylococcal antibiotics and for virulence. Although all the strains were very susceptible, the one chosen seemed to be somewhat more so than the rest.

All of the organisms used for infection were grown on proteose No. 3 agar (Difco) for 24 to 48 hours at 37 C. They were washed off into an equal mixture of 0.158 M Na Cl and 0.158 M sodium phosphate at pH 7.4. The cell suspensions were washed at least four times in an attempt to remove all loosely adsorbed antibiotic or diphtheria toxin. After being adjusted to the appropriate concentrations, staphylococcal and diphtheria suspensions were mixed immediately prior to the injection. The mixtures were all given to the animals within a matter of one to four minutes. In the principal study the injections were made by the subcutaneous route, while in one series of tests the intracutaneous site was utilized. For the subcutaneous infection, a volume of 1 ml. was given. This contained an average of 165×10^6 diphtheria organisms and 730×10^6 staphylococci. The organism dosage varied within fairly narrow limits.

In a few experiments the mixtures were given intratracheally. In these limited tests, the guinea pigs were first anesthetized lightly with pentobarbital (Nembutal) intraperitoneally and then given ether. The trachea was bared; a thread was drawn under it, and injections were made directly into the lumen while it was stabilized by pulling the thread upward. Direct injections through the unbroken skin into the trachea proved too difficult to achieve with certainty.

In many of the experiments, control animals were given prophylactic antitoxin to make certain of the cause of the lethal outcome. For this purpose, 2,000 units of commercial diphtheria antitoxin (Lederle) was given intraperitoneally 5 to 24 hours prior to the infections. The guinea pigs were albino females, weighing from 300 to 350 gm. They were all purchased from one dealer.

* Dr. Margaret Holden provided this culture.

Results

A total of 29 staphylococcal strains were tested in mixed infections by the subcutaneous route. These showed varying degrees of in vitro antibiotic activity against the diphtheria strain used in the tests. These data and the results of the mixed infections are summarized in Table 1. It may be seen that high degree of protection against lethal outcome was obtained with all but one of the Staphylococcus strains which inhibited the diphtheria culture in vitro more than 4.4 mm. under the assay conditions. Staphylococcal strains that were without in vitro activity or which produced smaller inhibition zones were without any effect on the lethal outcome. The vast majority of the deaths occurred in the first to the third day. Survival time for the mortality figures was recorded as final after 14 days. Many of the experiments were followed for as long as 30 days without any significant change in the results. The data also reveal that the staphylococcal cultures themselves were nonlethal. In fact, very little local evidence of infection was seen in most of the animals receiving the staphylococci alone. The five strains which afforded protection and whose antibiotic had been analysed previously were of Groups I and II.[2] Strain 431-5, which showed a high degree of in vitro activity, was quite without in vivo effect in this system. It is of much interest that this strain produced an antibiotic of Group V. In connection with this, it may be pointed out that the strains of lesser in vitro potency were of other antibiotic groups.

Another series of experiments was carried out, in which the mixed infections were given intracutaneously. The results of these tests are shown in Table 2. Only one high-

TABLE 1.—*Mixed Staphylococcus-Diphtheria Infection in Guinea Pigs (Subcutaneous)*

Ocular Staphylococcus Component	Antibiotic Activity of Staph. vs. C. Diphtheriae	Antibiotic Group	Results of Mixed Infections		Staphylococcus Controls, Survivors/ Total Injected
			Survivors*/Total Injected	%	
None, diphtheria alone	----	----	0/20	0	----
None, diphtheria antitoxin	----	----	18/20	90	----
K88-8	8.4†	----	11/11	100	2/2
K609-16	8.3	----	7/8	90	4/4
K102-11	8.1	----	7/7	100	2/2
117-3	8.1	I	16/16	100	8/8
K423-11	7.4	----	7/7	100	2/2
K618-6	7.2	----	7/8	90	3/4
K17-5	7.0	I	10/12	85	6/6
K610-18	6.9	----	8/8	100	4/4
431-5	6.5	V	0/8	0	4/4
188-4	6.4	I	8/8	100	3/4
100-5	6.0	I	7/8	90	4/4
455-1	4.4	II	9/12	75	6/6
290-7	4.1	IX	0/8	0	3/4
191-4	2.4	VII	0/16	0	10/10
224-4	2.1	III	0/8	0	4/4
212-1	2.0	----	0/4	0	2/2
81-5	1.0	VII	0/8	0	4/4
127-1	0	----	0/8	0	3/4
280-3	0	----	0/8	0	4/4
223-1	0	----	0/8	0	4/4
217-1	0	----	0/8	0	3/4
K887-5	0	----	0/3	0	----
K582-7	0	----	0/3	0	----
K595-1	0	----	0/3	0	----
K1758-2	0	----	0/4	0	2/2
K1084-17	0	----	0/3	0	----
K1796-1	0	----	0/4	0	2/2
K661-1	0	----	0/3	0	----
K609-1	0	----	0/4	0	2/2

* Survival time used was 14 days.
† The figures represent the zone of inhibition of the mitis strain used for infection. They are average values of a number of assays.

ly active and one nonactive Staphylococcus strain were used here, and it may be seen that only the active strain, No. 96-6, conferred a high degree of protection against lethal outcome. In this series of tests a portion of the same suspension of strain 96-6 was heat-killed by subjection to a temperature of 70 C for one-half hour. This killed portion was mixed with the diphtheria suspension and injected exactly as in the previous groups. It may be noted that similar high degree of protection was obtained with the heat-killed suspension.

It was previously demonstrated that part of the antibiotic is either tightly adsorbed onto the bacterial cell body or is intracellular in a number of these strains.[2] Since the above studies were carried out with suspensions mixed immediately prior to injection, it was necessary to ascertain that there was no effect on the diphtheria organism in vitro. Accordingly, a number of tests were carried out in which the washed diphtheria suspension was mixed with an equal volume of heat-killed staphylococcal cells (70 C, one-half hour). This treatment of the latter did not affect the "adsorbed" antibiotic, since most of these agents were previously shown to be stable at 100 C for this length of time at neutral pH values. The diphtheria and

TABLE 2.—*Intracutaneous Mixed Staphylococcus-Diphtheria Infections of Guinea Pigs*

Group	Antibiotic Activity of Staph.*	Guinea Pigs, No.	Cumulative Deaths at Day			Total Deaths, %
			2	3-5	6-20	
C. diphtheriae+NaCl-PO$_4$	--	20	11	16	18	90
C. diphtheriae+antibiotic Staph. albus No. 96-6	7.0	24	2	2	2	8
C. diphtheriae+Nonantibiotic Staph. albus No. 127-1	0	20	10	14	16	80
C. diphtheriae+heat-killed antibiotic Staph. No. 96-6.	--	20	0	0	1	5
C. diphtheriae+antitoxin	--	11	0	0	0	0

* Zone of inhibition of the C. diphtheriae strain used for infection in millimeters.

TABLE 3.—*Effect of Exposure of Washed C. Diphtheriae Mitis to Crude Staphylococcal Antibiotics and to Washed Heat-Killed Staphylococcal Cells*

Staphylococcal Strain	Inhibition of C. Diphtheria by Living Staphylococcus	Mixture	Viable Counts of C. Diphtheriae, Colonies/Ml.	
			At 0 Hr.	At 2 Hr.
96-6	6.7	Diphtheria-buffer	66×10⁶	67×10⁶
		Diphtheria-killed 96-6 staphylococci	35×10⁶	70×10⁶
		Diphtheria-crude 96-6 antibiotic	55×10⁶	68×10⁶
117-3	8.3	Diphtheria-buffer	8×10⁶	11×10⁶
		Diphtheria-killed 117-3 staphylococci	18×10⁶	31×10⁶
		Diphtheria-crude 117-3 antibiotic	12×10⁶	31×10⁶
K88-8	7.5	Diphtheria-buffer	28×10⁶	15×10⁶
		Diphtheria-killed K88-8 staphylococci	16×10⁶	19×10⁶
		Diphtheria-crude K88-8 antibiotic	20×10⁶	20×10⁶
290-7	3.7	Diphtheria-buffer	35×10⁶	58×10⁶
		Diphtheria-killed 290-7 staphylococci	61×10⁶	50×10⁶
		Diphtheria-crude 290-7 antibiotic	2×10⁶	0.2×10⁶
191-4	3.5	Diphtheria-buffer	23×10⁶	20×10⁶
		Diphtheria-killed 191-4 staphylococci	13×10⁶	14×10⁶
		Diphtheria-crude 191-4 antibiotic	0.5×10⁶	0.1×10⁶

heat-killed staphylococcal cell suspension mixtures were allowed to stand at room temperature for two hours, with plate counts of the viable diphtheria cells being made at intervals. In other tubes equal volumes of potent crude antibiotic solutions from the various strains were added to the original suspension of corynebacteria and plate counts also were made. The type of results obtained with some of these strains is shown in Table 3. It may be seen that the first three staphylococcal strains listed showed no effect on the viability of the washed diphtheria cells after prolonged exposure to the crude antibiotic or to the killed bacterial cells. These strains were highly protective in vivo. It is thus clear that these antibiotics could not have damaged the diphtheria cells in the few minutes which elapsed between the mixing of the cultures and the injections. The situation was somewhat different with Strains 290-7 and 191-4. Although the heat-killed cells had no effect on the diphtheria viability, the crude antibiotic reduced the count about tenfold immediately and about one-hundredfold after two hours. These latter two strains were without in vivo protective activity. That the heat-killed cells of the first three staphylococcal strains in Table

TABLE 4.—*Antibiotic Assay of Washed and Heat-Killed Antibiotic-Producing Staphylococcal Cells*

Staphylococcal Strain	Inhibition of C. Diphtheria by Living Staphylococcus, Mm.	Preparation	Inhibition Zone vs. C. Diphtheriae, Mm.				
			Undiluted	10^{-1}	10^{-2}	10^{-3}	10^{-4}
96-6	6.7	Killed cells,	4.3	2.2	0	0	0
		crude antibiotic	6.1	3.3	1.0	0	0
117-3	8.3	Killed cells,	10.4	9.4	5.4	1.9*	0
		crude antibiotic	10.4	7.5	4.1	0	0
K88-8	7.5	Killed cells,	7.0	2.6	0	0	0
		crude antibiotic	13.0	6.9	2.4	0	0
290-7	3.7	Killed cells,	0.0	0	0	0	0
		crude antibiotic	6.6	3.9	1.0	0	0
191-4	3.5	Killed cells,	0	0	0	0	0
		crude antibiotic	10.5	6.4	2.0	0	0

* Inhibition zone poorly demarcated.

TABLE 5.—*Production of Antibiotic by Staphylococcus Albus No. 96-6 on Various Media*

Agar Medium*	Antibiotic Activity of Crude Supernate vs.		
	Staph. Albus No. 7-6	C. Pseudodiphtheriae A6485	C. Diphtheriae Mitis (H)
Nutrient	2.6†	10.5‡	11.2
Nutrient agar-0.5% glucose	2.6†	8.9	8.9
M.R.-V.P.	2.7†	9.5	8.3
Potato infusion	2.6†	9.9	10.5
Heart infusion	3.1	10.8	11.1
Beef lactose	3.9	10.3	8.6
Nutritive caseinate	2.7†	8.2	6.9
Trypsin digest	2.2†	7.0	7.2
Brain-heart infusion	2.7	13.5	6.9
Endameba	1.7	12.8	7.0
Proteose No. 3	2.8	15.6	10.3
Proteose No. 3-0.5% glucose	2.0	13.7	6.3
Proteose No. 3-1% lactose	3.0	16.4	11.7
Proteose No. 3-1% sucrose	2.2	14.0	9.2
Proteose No. 3-1% maltose	3.1	15.2	8.0
Tryptone glucose extract	2.9†	8.8	11.8
Proteose tryptone	2.3	17.8	12.7
Cystine heart	2.5	18.0	9.1
Staphylococcal medium No. 110	3.5	15.7	9.5

* All of the media used were products of the Difco Laboratories.
† Partial inhibition zones.
‡ Zone of inhibition (mm.) from edge of well to beginning of normal growth.

3 did contain cellular antibiotic and that the other two did not is demonstrated in Table 4. The killed cells and crude antibiotics of these strains were assayed in serial dilutions on agar plates against C. diphtheria mitis (H). Relatively large amounts of the active substance were found tightly associated with the cells of the first three strains, in comparison with the potency of the crude supernates.

In those instances where in vivo protection was obtained, it is certain therefore, that the action actually took place in the tissues. Because it would appear from the data in Tables 2 and 4 that the protection obtained could be accounted for by the cellular staphylococcal antibiotic injected in the mixture, a search was made for a medium in which antibiotic was not produced. Protection obtained with mixed infections using such suspensions would be unequivocally due to in vivo synthesis of antibiotic. Attempts to find a medium which gave good growth of the staphylococci without significant antibiotic production were unsuccessful. A partial list of the media tried out is shown in Table 5. It may be seen that all of the media gave crude antibiotic of approximately the same potency with this strain. Similar good production of antibiotic in liquid media was found.

Because the subcutaneous and intracutaneous routes were rather unrelated to the usual upper respiratory infection site with diphtheria, a few tests were carried out with intratracheal injections of these mixtures, as providing a closer approach to the normal habitat. In orienting tests it was found that a large dose of diphtherial cells was necessary for a lethal outcome by this route. The results obtained in two experiments using this approach are shown in Table 6. The

TABLE 6.—*Mixed Diphtheria-Ocular Staphylococcal Infections by the Intratracheal Route*

Infective Mixture	Results of Mixed Infections		Results of Control Staphylococcal Infections	
	Exper. 1.	Exper. 2.	Exper. 1.	Exper. 2.
Diphtheria & buffer	D1 D2 D2 D2 D4	D1 D2 D2 D2	....	....
Diphtheria & antitoxin	D2 D2 8* 8 8	D13 8 8 8	....	....
Diphtheria & antibiotic staphylococcus 117-3	D1 D2 D3 8 8	D6 8 8 8	8 8 8 8 8	D2 8 8 8
Diphtheria & nonantibiotic staphylococcus 127-1	D1 D1 D1 D1 D2	D1 D2 D2 D3	8 8 8 8 8	8 8 8 8

* 8, Survived one month.

injections were all made in a volume of 0.1 ml. For the first experiment, the doses of the organisms given were as follows: diphtheria, 360×10^6; active Staphylococcus, 117-3 strain, 800×10^6, and nonactive Staphylococcus, 600×10^6. For the second test, the doses were 110×10^6, 600×10^6, and 400×10^6, in the same order. The results suggest that some protection was obtained by the antibiotic staphylococci. That the lethal outcome was due to diphtheria was indicated by the protection obtained by antitoxin. The nonantibiotic strain was completely ineffective, and the guinea pigs given this mixture all died. The almost complete survival of the staphylococcal control animals reveals that the technique itself did not cause death and also that the staphylococci were of low virulence by this route. These control animals had received the same doses of staphylococci as the group getting mixed infections. The animals which died after receiving diphtheria suspension alone or mixed with staphylococci were autopsied in a number of instances. Extensive red pneumonic consolidation was observed grossly.

Comment

This study has demonstrated the protection obtained by antibiotically active staphylococci against lethal outcome in diphtheria infections of guinea pigs. These results confirm limited observations reported by Duliscouët,[23] who used a single antibiotic staphylococcal strain isolated from the nasopharnyx. The organisms used here were all isolated from human ocular flora. Although it is clear that protection was obtained by active strains, it is not clear that in vivo production of antibiotic is the mechanism involved. In the single instance in which a heat-killed antibiotic producer (96-6) was used, the protection found was of the same order of magnitude as was that noted with this living staphylococcal culture. In previous studies with mixed infections with these strains and C. septicum spores in mice[24] evidence was presented along these lines that did indicate in vivo production of antibiotic. In this current work with diphtheria, in addition, one strain highly active in vitro had no effect in vivo in this system.

For an ideal in vivo study it would have been preferable to use organisms which were completely free of tightly adsorbed or intracellular antibiotic. Attempts were made to grow one of these organisms on a large variety of media under differing conditions to achieve this end, and all attempts were unsuccessful. Antibiotic was produced in abundance whenever growth occurred. It is certain, however, that the protection observed was a result of antibiotic action within the tissues, as allowing washed mixtures of the diphtheria suspension and antibiotic-producing Staphlyococcus to stand at room temperature for as long as two hours had no observable effect on the viability of the corynebacteria. The crude antibiotics tested in similar circumstances also were without an antibacterial effect, except for the two strains examined which had no in vivo activity. It should be recalled that the organism suspensions were used within one to five minutes after mixing.

The limited data obtained with the intratracheal inoculations are of interest. This route does represent a somewhat closer approach to the natural habitat of these organisms, and a suggestion of protection was found with the highly active Staphylococcus. That the lethal outcome was due to diphtheria was indicated by the protection found with antitoxin and the lack of lethal effect of the staphylococci alone. Unfortunately, the tediousness of the inoculation technique made larger and more adequate experiments impractical. Although the mixtures of diphtheria bacilli and staphylococci were made just prior to inoculation in these tests as well, there was a possibility that the washed diphtherial cells would deteriorate spontaneously during the course of an experiment which lasted up to two and one-half hours. For this reason, all of the control animals which received diphtheria alone were inoculated at the end of the procedure.

Summary

Guinea pigs were infected subcutaneously with mixtures of washed Corynebacterium diphtheriae mitis and ocular staphylococci. When the staphylococcal component produced potent antibiotic active against the diphtheria bacilli, protection against lethal outcome was obtained in most instances. Nonactive or slightly active staphylococci were without effect on the mortality rates.

The staphylococcal strains by themselves were all essentially avirulent, and they did not cause an appreciable number of deaths.

No significant effects on the viability of the diphtheria cells were found in mixtures of washed diphtheria bacilli and heat-killed antibiotic staphylococci after they had stood at room temperature for two hours. Under these conditions the diphtheria cells were not affected by crude antibiotic from several strains highly protective in vivo.

Preliminary tests suggest that lethal intratracheal diphtheria infections can be produced, and this route may offer some advantages in these studies.

College of Physicians and Surgeons, Columbia University.

REFERENCES

1. Halbert, S. P., and Swick, L. S.: Antibiotic-Producing Bacteria of the Ocular Flora, Am. J. Ophth. 35:73-81 (May, Pt. 2) 1952.

2. Halbert, S. P.; Swick, L. S., and Sonn, C.: Characteristics of Antibiotic Producing Strains of the Ocular Flora, J. Immunol. 70:400-410, 1953.

3. Halbert, S. P.; Swick, L.; Sonn, C., and Locatcher-Khorazo, D.: Ocular Antibiotic-Producing Bacteria in Normal Eyes and in Conjunctivitis, A. M. A. Arch. Ophth. 51:7-14, 1954.

4. Halbert, S. P.; Locatcher-Khorazo, D.; Kazar, C. S., and Swick, L. S.: Further Studies on the Incidence of Antibiotic-Producing Micro-Organisms of the Ocular Flora, A. M. A. Arch. Ophth., to be published.

5. Gratia, A.: Sur un remarquable exemple d'antagonisme entre 2 souches de colibacille, Compt. rend. Soc. biol. 93:1040-1041, 1925.

6. Gratia, A.; Fredericq, P.; Joiris, E.; Betz-Barreau, M., and Weerts, E.: La Technique de la "double couche" de gelose, et la distribution des germes producteurs de colicines dans les matières fécales normales et pathologiques de l'homme et des animaux, Antonie van Leeuwenhoek 16:31-37, 1950.

7. Fredericq, P.: Actions reciproques chez les enterobacteriaceae, Rev. belge path. et méd. expér. 19 (Supp. 4): 1-107, 1948.

8. Halbert, S. P.: The Antagonism of Coliform Bacteria Against Shigella, J. Immunol. 58:153-167, 1948.

9. Halbert, S. P., and Gravatt, M.: Prevalence of Antibiotic-Producing Coliform Organisms, Pub. Health Rep. 313-318, 1949.

10. Evans, C. A.; Smith, W. M.; Johnston, E. A., and Gilbert, E. R.: Bacterial Flora of the Normal Human Skin, J. Invest. Dermat. 18:305-324, 1950.

11. Murray, R. G. E., and Loeb, L. J.: Antibiotics Produced by Micrococci and Streptococci That Show Selective Inhibition Within the Genus Streptococcus, Canad. J. Res. 28:177-185, 1950.

12. Üri, J.; Szabó, G., and Oláh, D.: Production of Antibiotics by Dermatophytons, Acta. physiol. Acad. sc. hung. 5:255-260, 1954.

13. Jennings, M. A., and Sharp, A. E.: Antibacterial Activity of the Staphylococcus, Nature, London 159:133-134, 1947.

14. Sherwood, N., and van der Smissen, E.: The Incidence of Bacteria in the Tonsillar and Nasopharyngeal Areas Showing an Inhibitory Effect on Certain Beta Hemolytic Streptococci: Unpublished Report to the Missouri Valley Branch of the Society of American Bacteriologists, April, 1950, personal communication to the authors.

15. Scrivener, C. A.; Myers, H. I.; Moore, N. A., and Warner, B. W.: Some Antagonistic Activity of Bacteria from the Human Oral Cavity, J. Dent. Res. 29:784-790, 1950.

16. Scrivener, C. A.; Myers, H. I.; Moore, N. A., and Warner, B. W.: Frequency of Micro-Organisms That Influence Lactobacillus Growth in Vitro, J. Dent. Res. 30:665-669, 1951.

17. Heatley, N. G., and Florey, H. W.: An Antibiotic from Bacterium coli, Brit. J. Exper. Path. 27:378-390, 1946.

18. Halbert, S. P., and Magnuson, H. J.: Studies with Antibiotic Producing Strains of Escherichia Coli, J. Immunol. 58:387-415, 1948.

19. Gardner, J. F.: Some Antibiotics Formed by Bacterium Coli, Brit. J. Exper. Path. 31:102-111, 1950.

20. Halbert, S. P.: The Relation of Antagonistic Coliform Organisms to Shigella Infections: I. Survey Observations, J. Immunol. 60:23-36, 1948.

21. Halbert, S. P.: The Relation of Antagonistic Coliform Organisms to Shigella Infections: II. Observations in Acute Infections, J. Immunol. 60:359-381, 1948.

22. Mondolfo, H.: El Antagonismo entre las baterias intestinales y su importancia desde el punto de vista higienico, An. méd. púb. 1:219-232, 1949.

23. Duliscouët, R., and Ballet, B.: Curieuses propriétés des staphylocoques chez les porteurs de bacilles diphtériques: Indications pronostiques et applications thérapeutiques, Presse méd. 43:1297-1300, 1935.

24. Halbert, S. P.; Sonn, C., and Swick, L. S.: Mixed Bacterial Infections in Relation to Antibiotic Activities: I. Clostridium Septicum-Micrococcus Infections, J. Immunol. 73:169-179, 1954.

25. Halbert, S. P.; Sonn Kazar, C., and Swick, L. S.: Mixed Bacterial Infections in Relation to Antibiotic Activities: II. The Role of Staphylococcal Antibiotic in a Clostridium Septicum-Staphylococcus Albus Infection, Antibiotics & Chemmother., to be published.

26. Dunnington, J. H., and Locatcher-Khorazo, D.: Value of Cultures Before Operation for Cataract, Arch. Ophth. 34:215-219, 1945.

Oxygen Studies in Retrolental Fibroplasia

V. The Effect of Rapid vs. Gradual Withdrawal from Oxygen on the Mouse Eye

ARNALL PATZ, M.D., and ANN B. EASTHAM, Baltimore

It is now generally accepted from abundant clinical [1,2] and experimental [3-5] data that the over-use of oxygen is an important and probably the principal factor in the development of retrolental fibroplasia. There are, however, several controversial factors which are thought to influence the action of oxygen on the premature retina. One of these is the rate of withdrawal from the initial exposure to oxygen. Prolonged gradual withdrawal from oxygen to minimize or avoid the retinal damage produced by oxygen has been advocated principally by Szewczyk [6] and Bedrossian and co-workers.[7]

This report is based on experiments designed to evaluate the effect of gradual versus rapid withdrawal from oxygen in the mouse eye. The data show that the additional oxygen administered during a period of gradual withdrawal frequently represented that added amount of oxygen necessary to make an initial nontoxic exposure to oxygen injurious.

Subjects and Methods

Experiment I.—Four litters of newborn white mice were placed in the oxygen incubator at 80% concentration for 24 hours. One-half of the animals were then abruptly removed to room air (20% oxygen), and the remaining half of the animals, paired off as litter mates to those already removed, were kept in the incubator. The animals in the incubator were subjected to a gradual reduction in oxygen concentration at the rate of 10% concentration reduction daily. On the seventh day the concentration of room air was reached and the animals were removed from the incubator and placed in holding cages. All animals were killed on the 16th day of age.

The results of this experiment are shown in Figure 1. None of the animals which were abruptly removed from the chamber after one day's exposure showed any ocular abnormality. In those eight animals gradually removed from oxygen, 4 of the 16 eyes showed ocular lesions. These consisted of intraocular hemorrhages, abnormal persistence and proliferation of the hyaloid system, and retinal hemorrhages.

Experiment II.—Litters of newborn mice were placed into the incubator as in Experiment I. Twelve newborn animals were exposed to an oxygen concentration of 80% for 48 hours. One-half of the young animals

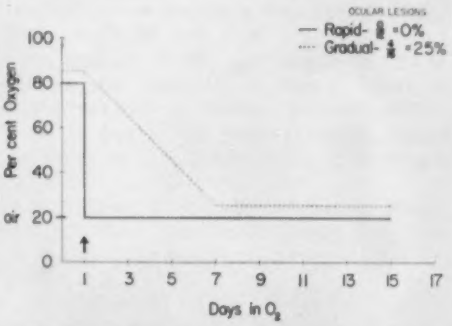

Fig. 1.—Schematic diagram of oxygen concentrations in Experiment I. Note absence of ocular lesions in animals rapidly withdrawn from oxygen.

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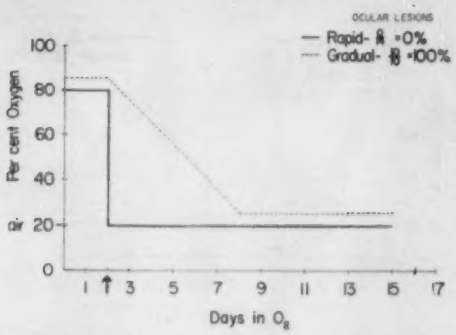

Fig. 2.—Schematic diagram of oxygen concentrations in Experiment II. Note absence of ocular lesions in animals rapidly withdrawn.

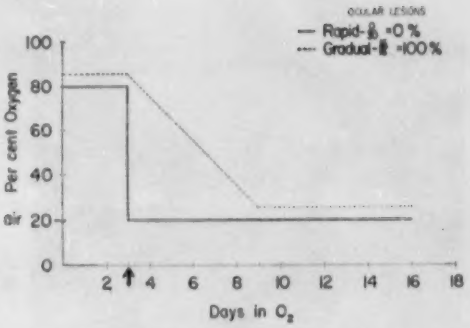

Fig. 3.—Schematic diagram of oxygen concentrations in Experiment III. Note absence of ocular lesions in animals rapidly withdrawn.

were then abruptly removed to room air. The remaining half of the animals, matched as litter mates to those rapidly removed, were kept in the incubator. The oxygen concentration in the incubator was then gradually reduced at a rate of 10% per day over six days. The animals were then at a room air concentration on the eighth day and were then removed to cages in room air. All animals were killed on the 16th day of age.

The results of this experiment are shown in Figure 2. Twelve young animals survived the experiment. In the seven animals (14 eyes) which were rapidly removed from oxygen, there were no ocular lesions. In the five animals (10 eyes) that were gradually weaned from 80% oxygen over a six-day period, 100% of the eyes showed ocular lesions. These consisted of intraocular hemorrhages, abnormal persistence and proliferation of the hyaloid, and abnormal retinal vascular tufts proliferating from the nerve fiber layer of the retina into the vitreous.

Experiment III.—Newborn litters of mice were placed into the incubator as in the above experiments. The animals were exposed to an initial concentration of 80% for three days. During this experiment foster mother animals were exchanged with the animals in the incubators to prevent pulmonary edema in the exposed mother animals. The mother animals were exchanged every 24 hours. After three days of exposure to 80% oxygen, one-half of the young were abruptly removed to room air. The remaining half of the young animals, matched as litter mates to those rapidly removed, were kept in the incubator for an additional six days. The oxygen was gradually reduced in the incubator at a rate of 10% per day, to reach the concentration of room air on the ninth day. The animals were then removed to cages in the laboratory.

The results of Experiment III are shown in Figure 3. Of 15 animals surviving the rapid withdrawal from oxygen, none (30 eyes) showed any ocular lesions. In the eight animals (16 eyes) which survived the gradual withdrawal from oxygen, all eyes showed ocular lesions. These consisted of intraocular hemorrhages, abnormal persistence and proliferation of the hyaloid vessels, retinal hemorrhages, and capillary tufts proliferating from the retina into the vitreous. All animals were killed on the 16th day of age.

Experiment IV.—Litters of newborn mice were placed in the incubators as in the above experiments. The mother animals were exchanged every 24 hours with foster mothers as in Experiment III. All the young animals were exposed to an initial concentration of oxygen of 80% for a period of four days. One-half of the animals were then abruptly removed to room air. The remaining half of the animals, matched as litter mates to those rapidly removed, were kept in the incubator. The oxygen concentration was then gradually reduced at a rate of 10%

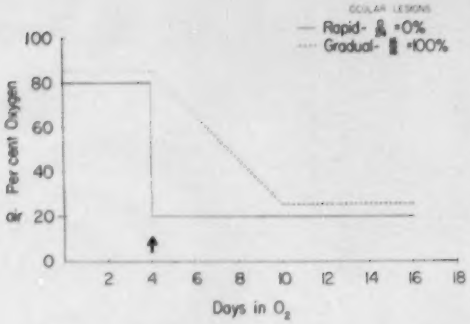

Fig. 4.—Schematic diagram of oxygen concentrations in Experiment IV. Note absence of ocular lesions in animals rapidly withdrawn.

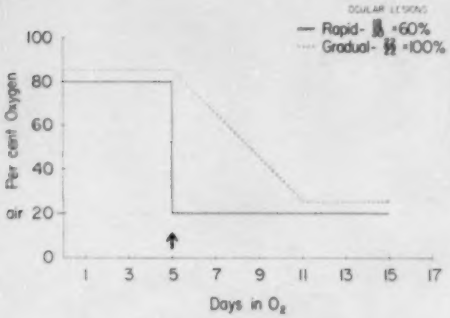

Fig. 5.—Schematic diagram of oxygen concentrations in Experiment V. For the first time, lesions are detected after rapid withdrawal from oxygen.

daily so that on the 10th day the incubator concentration was that of room air (20%). The animals were then removed from the incubators and placed into cages in the laboratory. All animals were killed on the 16th day.

The results of this experiment are shown in Figure 4. In the 12 animals (24 eyes) which survived the rapid withdrawal from oxygen, there were no ocular lesions observed. In the eight animals which survived the gradual withdrawal from oxygen (16 eyes), all eyes showed ocular lesions. These consisted of intraocular hemorrhages, abnormal persistence and proliferation of the hyaloid system, retinal hemorrhages, and retinal capillary tufts proliferating into the vitreous.

Experiment V.—Litters of newborn mice were placed in the incubator as in the above experiments. Mother animals were exchanged at 24-hour intervals with foster mothers as described above. All young mice were exposed to oxygen at 80% concentration for an initial period of five days. One-half of the animals were then abruptly removed to room air. The remaining half, which were matched as litter mates to those removed rapidly, were then kept in the incubator. The oxygen concentration in the incubator was gradually reduced at a rate of 10% daily from 80% to room air (20%) over a period of six days, and on the 11th day the animals in the incubator were transferred to cages in room air. All animals were killed on the 16th day.

The results of this experiment are shown in Figure 5. Fifteen animals survived the rapid withdrawal portion of the experiment. Of these 15 animals (30 eyes), 18 eyes showed ocular lesions. These consisted of intraocular hemorrhages, abnormal persistence and proliferation of the hyaloid system, and proliferation of retinal vessels into the vitreous. Eleven animals (22 eyes) survived the gradual withdrawal from oxygen. In all 22 eyes ocular lesions were noted, and these consisted of the same lesions just mentioned in the animals rapidly withdrawn. It was significant to note that the severity of lesions in the group from which oxygen was gradually withdrawn exceeded in each case the maximum degree of ocular lesions observed in any of the animals rapidly withdrawn.

Experiment VI.—Litters of newborn mice were placed in the incubator at 80% oxygen concentration for seven days, with use of foster mothers as in Experiment V. One-half of the young were abruptly removed to room air after seven days. The remaining half, which were matched as litter mates to those removed abruptly, were kept in the incubator. The oxygen concentration was gradually reduced at a rate of

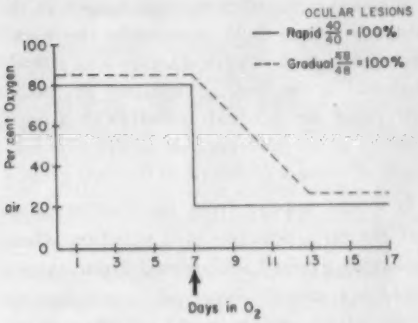

Fig. 6.—Schematic diagram of oxygen concentrations in Experiment VI. There is no difference between the groups in incidence of lesions after seven days in oxygen.

10% daily over a period of six days. All animals were killed at 16 days of age.

The results of this experiment are shown in Figure 6. Twenty animals survived in the rapid withdrawal group. Ocular lesions were found in 100% (40 eyes), as described in Experiment V. Twenty-four animals survived the gradual withdrawal experiment. In all 24 animals (48 eyes) ocular lesions as described in Experiment V were detected. There was no difference in severity of lesions in the animals of the rapid and the gradual withdrawal group.

Comment

Bedrossian and co-workers[7] are to be commended for having performed a controlled study on rapid versus gradual withdrawal from oxygen in the nursery. Their data suggested that gradual withdrawal from oxygen offered protection from the damaging effect of the initial exposure to oxygen. It would be highly desirable to have these studies extended to involve a much larger number of infants. It is obvious that their experiments cannot now be further studied clinically in view of the now well-established toxicity of oxygen for the infant eye. Since the problem cannot be further evaluated, for ethical reasons, in a controlled nursery study, we must now rely on animal experimentation to elucidate this question.

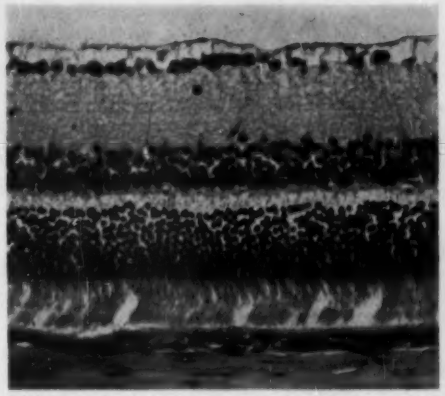

Fig. 7.—Retina of normal 16-day-old mouse raised in room air as control; reduced from mag. × 450.

Fig. 8.—Typical endothelial proliferation on surface of retina of mouse gradually withdrawn from oxygen in Experiment III; reduced from mag. × 450.

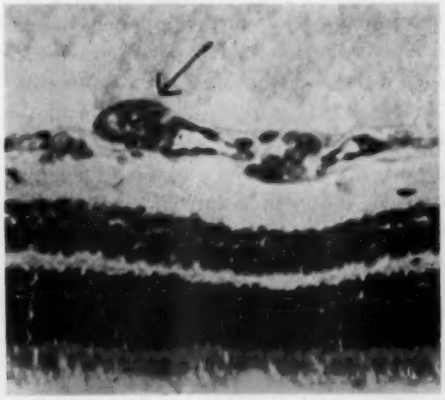

Fig. 9.—Section showing persistence and proliferation of hyaloid vessels (H. V.) and large hemorrhages (H.) in oxygen-treated mouse; reduced from mag. × 30.

Before applying the data from these experiments to the problem of oxygen administration in the premature nursery, one must be extremely cautious in translating these results to the problem of human retrolental fibroplasia (RLF). However, the ability to produce, in animals with immature retinas, lesions almost identical histologically to those of early human RLF justifies a reasonable degree of confidence in applying animal data to the human problem.

Exposure of mice to 80% oxygen concentration for a period up to four days was nontoxic when the animals were immediately removed to air (Fig. 4). Yet when mice were in 80% oxygen for only two days (Fig. 2) and gradually withdrawn from 80% oxygen to room air, all animals showed ocular lesions. Gradual withdrawal from oxygen, instead of minimizing the ocular effect of oxygen, furnished the added amount of oxygen necessary to make an initial nontoxic dose damaging.

These animal data on the effect of rapid versus gradual withdrawal show one particular principle which suggests a practical clinical application. These data suggest that, following an initial nontoxic exposure of the infant to oxygen, the added oxygen that might be administered during a period of gradual withdrawal could furnish that extra amount of oxygen needed to make the total exposure injurious to the infant's retina.

The results of these experiments show very strikingly the importance of "duration" of exposure to oxygen on the immature mouse eye. Exposure at concentrations of 80% produced no observable ocular effect when the animals were removed within four days. However, the exposure of one additional day (Experiment V) resulted in ocular lesions in 60% of the animal eyes. After the animals had been exposed for seven days, it appeared that maximal damage had been produced and no difference in incidence or severity of lesions was noted in the rapid as compared with the gradual withdrawal group.

When the exposure was prolonged in the mouse to seven days, apparently the maximum amount of oxygen damage was already produced at the time of splitting the litters into rapid or gradual withdrawal groups. There was no difference in severity or incidence of lesions observed in the two groups.

It would appear from these animal data that the only possible safe situation where prolonged gradual withdrawal from oxygen would not actually cause additional damage to the infant retina would be when maximum damage had already been produced by the initial exposure to oxygen. During our controlled study [2,8] infants in the high-oxygen group were placed in 70% oxygen continuously for 30 days or longer. Many of these cases showed total and irreversible obliteration of the retinal vascular tree. The large vessels appeared as fine threads without blood columns. Even after the infant was kept in room air for as long as three hours after removal from the incubator, the vascular tree remained as attenuated threads. Here one can assume that maximal oxygen damage (vaso-obliteration) had been produced. Gradual withdrawal from oxygen would, therefore, not be expected to cause additional damage to the retinal vessels. Here, and here only, would it appear to be a safe procedure to engage in a practice of gradual reduction of oxygen in the incubator. However, it is extremely unlikely under current practices that infants would be maintained for such long periods at sufficiently high levels of oxygen to obliterate totally the retinal vessels.

Gyllensten and Hellström's recent observations [9] on the effect of gradual transfer of animals from oxygen to air led them to conclude that a procedure of gradual withdrawal does not prevent oxygen-induced ocular lesions. The main difference that they noted between animals gradually transferred to air and those rapidly transferred was the time schedule of appearance of ocular lesions.

Summary and Conclusions

Experiments conducted on young mice demonstrated that prolonged gradual withdrawal from an initial high concentration of oxygen does not prevent the production of ocular lesions produced by oxygen. On the contrary, in some experiments gradual withdrawal increased both the severity and and the frequency of ocular lesions.

These mouse experiments show that the additional oxygen that was administered in the period of gradual withdrawal from oxygen frequently represented the added amount of oxygen that was necessary to make an initial nontoxic exposure injurious to the animal eye.

The possible nursery application of these data is briefly discussed.

1212 Eutaw Place (17).

REFERENCES

1. Kinsey, V. E.: Etiology of Retrolental Fibroplasia and Preliminary Report of Cooperative Study of Retrolental Fibroplasia, Tr. Am. Acad. Ophth. 59:15-24 (Jan.-Feb.) 1955.

2. Patz, A.; Hoeck, L. E., and De La Cruz, E.: Studies on the Effect of High Oxygen Administration in Retrolental Fibroplasia: I. Nursery Observations, Am. J. Ophth. 35:1248-1253 (Sept.) 1952.

3. Gyllensten, L. J., and Hellstrom, B. E.: Retrolental Fibroplasia: Animal Experiments, Acta pædiat. 41:577-582 (Nov.) 1952.

4. Ashton, N.; Ward, B., and Serpel, G.: Role of Oxygen in the Genesis of Retrolental Fibroplasia, Brit. J. Ophth. 37:513-520 (Sept.) 1953.

5. Patz, A.; Eastham, A.; Higgenbotham, D. H., and Kleh, T.: Oxygen Studies in Retrolental Fibroplasia: II. The Production of the Microscopic Changes of Retrolental Fibroplasia in Experimental Animals, Am. J. Ophth. 36:1511-1522 (Nov.) 1953.

6. Szewczyk, T. S.: Retrolental Fibroplasia and Related Ocular Diseases, Am. J. Ophth. 36:1336-1361 (Oct.) 1953.

7. Bedrossian, R. H.; Carmichael, P., and Ritter, J.: Retinopathy of Prematurity and Oxygen, Am. J. Ophth. 37:78-86 (Jan.) 1954.

8. Patz, A.: Oxygen Studies in Retrolental Fibroplasia: IV. Clinical and Experimental Observations, Am. J. Ophth. 38:291-308 (Sept.) 1954.

9. Gyllensten, L. J., and Hellström, B. E.: Experimental Approach to the Pathogenesis of Retrolental Fibroplasia: IV. The Effects of Gradual and of Rapid Transfer from Concentrated Oxygen to Normal Air on the Oxygen-Induced Changes in the Eyes of Young Mice, Am. J. Ophth. 41:619-627 (April) 1956.

Fundamental Limitations of Radiophosphorus Counting Methods Used for Detection of Intraocular Neoplasm

JAMES F. O'ROURKE, M.D.; HUMPHREY PATTON, B.S., and ROBERT BRADLEY, B.S., Bethesda, Md.

Since Scarney and Crossin's[1] early report, much work has been done with Geiger tubes placed on the eye, and attempts have been made to estimate from this the distribution of radiophosphorus within.[1-8,11,12,27] To date, the evidence recorded in favor of this technique for ocular tumor diagnosis appears to rest upon several broad assumptions. The experiments which follow were designed to examine certain of these assumptions and to secure, if possible, additional basic knowledge about the ocular uptake of P^{32}.

A preliminary phase of the study concerns measurement of the differential uptake by two ocular tumors of human origin, while the main part deals with the specific organ uptake by animal eyes, under conditions relevant to the clinical situation. Finally, an attempt was made to demonstrate the influence of scleral absorption upon external counting results.

One cannot claim that conclusions derived from animal experiments of this sort are entirely pertinent to the clinical problem. Properly interpreted, however, they may serve to direct the design of future clinical studies: As presented here they are intended to be indicative rather than definitive.

Methods

Freshly enucleated specimens were weighed and then immersed in 20 cc. of fuming nitric acid. The digestant was brought to a volume of 100 cc. with distilled water and thoroughly mixed. A 1.0 cc. aliquot was pipetted onto an aluminum planchet and dried under an infrared lamp.

Determinations of the gram tissue radiophosphorus content in microcuries (μc) were derived as follows:

$$\frac{\text{counts/min/gm. specimen}}{2.22\times10^{6}\ (\text{Emissions/sec/}\mu\text{c } P^{32})} \times \text{geometry} = \mu\text{c/gm. tissue.}$$

In computing these results a geometry factor of 9.0% obtained: This was derived by use of an end-window Geiger-Mueller tube, thickness 1.4 mg. per centimeter square of mica, and a Berkley Scaler, Model No. 2001, operating voltage 1,000 v. A Bureau of Standards Radium D and E standard source, No. 2385, was used and was covered with 7.20 mg. per centimeter square aluminum of approximately 0.001 in. thickness. Corrections advised for absolute beta counting were employed in the computation of this factor.[17]

The isotope uptake of an organ is conveniently expressed as its differential absorption ratio (D.A.R.). This term, devised by Marinelli and Kenney,[16] expresses the relationship of the organ content to that of whole body weight as follows:

$$\frac{\mu\text{c/gm. organ}}{\mu\text{c/gm. body weight}} = \text{D. A. R.}$$

Such a ratio will indicate whether an organ or tissue absorbs an amount of isotope sufficiently above the average for the entire body to make local detection feasible. The ratio is based on administered dose rather than retained dose, because it is not possible to measure the excretion of an iso-

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From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

tope accurately. The average excretion loss of 10% to 25% is not likely to invalidate findings computed this way.

In calculation of mean values for ratios and percentile figures we employed the harmonic mean method.[18]

Analyses of normal and experimentally inflamed eyes were made at intervals of 1 and 24 hours after intravenous injections of 50μmc of radiophosphorus per animal.

A total of 102 rabbit eyes were studied in five groups. Of the 24 globes in each of the four main groups, 12 were assayed at 1 hour, and 12, at 24 hours. One-half of the specimens in each group were obtained through bilateral enucleation: This permitted a limited study of uptake differences between the eyes of a single animal.

Injections were intravenous, and dilutions were made with sterile purified water. The 50μc dose represents a range of 15.5μc to 48.3μc per kilogram of rabbit weight; this is from two to six times the human adult dose of 500μc. Animals weighed from 1035 to 3205 gm., and the range of differences is approximately equal among the groups.

Radiophosphorus has a normal half-life of 14.3 days. Comparisons of 1-hour and 24-hour tissue levels included a correction for this decay factor.

Differential Uptake of Human Ocular Melanoma

There existed within the left globe of an adult white man a melanoma large enough to obscure almost all ophthalmoscopic view of the disk and macula. This mass occupied approximately one-fourth of the posterior chamber volume and extended from the ora serrata temporally to the paramacular region. During enucleation surgery, posterior perforation and tumor seeding of the adjacent orbital tissues were noted, and a subsequent exenteration was required.

Twenty-four hours after the administration of 500 μc of radiophosphorus to this patient, counts of both eyes were taken on a quadrant basis, with use of the bevelled Geiger counting tube (Anton 224). During surgery a curved posterior pole type of Geiger counter (Anton 225 probe) was placed over six separate areas of the temporal half of the tumor-bearing eye, including the site of posterior perforation. In both types of counting technique, we obtained no evidence of increased activity over the tumor. A second patient with a smaller posterior pole tumor (0.22 gm.) gave a similar counting result. In each case counting was done over both eyes preoperatively and over normal and tumor-bearing areas of the suspect eye during surgery. Each of the enucleated eyes was sectioned through the tumor site and again at the pars plana. The tumor masses were carefully dissected free from the posterior segments containing them. (Small slices were taken for pathologic study.) Separate assays were made of the tumors and of all posterior segment tissue except vitreous: This was done 24 hours after P^{32} injection. Methods of tissue analyses are detailed above. Table 1 contains the results of this tissue assay.

TABLE 1.—*Results of Tissue Analysis in Two Cases of Melanoma*

	Wt., Gm.	P^{32}, μc/Gm.	% of 500 μc Dose
I. Tumor	1.2	0.110	0.0220
Ocular tissue	1.98	0.010	0.0020
II. Tumor	0.226	0.053	0.0106
Ocular tissue	0.777	0.004	0.0008

These results were disturbing for two reasons. First, the tumor levels of P^{32} were only 10 and 13 times that of adjacent ocular tissues; this does not represent high specific uptake for small tumors and could be easily overlooked on external counting. Second, the globe itself (posterior two-thirds only) contained only 0.008% to 0.002% of the high P^{32} dose given (500μc); this is a very low specific uptake.

Differential Uptake of Normal Globe

The adequacy of external counting requires that the P^{32} content of conjunctiva and Tenon's fascia be less than that of the

globe. The following analyses (24 eyes) were done to determine what per cent of administered radiophosphorus resides in globes devoid of such tissue.

Twelve eyes were enucleated at each interval of 1 hour and 24 hours following injection of the isotope. The specimens were thoroughly cleaned of all external tissue, and counting samples were prepared in the manner described. Figure 1 and Table 2 depict the results expressed as millicuries per gram of tissue and mean D. A. R.

One hour mean D. A. R. values show an ocular uptake less than one-fifth of the whole body average, in globes cleaned of conjunctiva fascia and muscle.

Expressed as per cent of dose this low ocular uptake is yet more apparent (0.0040% to 0.0536%).

The 24-hour value for mean D. A. R. is a bit more than a half of the 1-hour level. This value and the per cent of dose figures agree approximately with those calculated for the two human eyes previously analyzed (Table 1).

Differential Uptake of Normal Globe with Conjunctiva and Muscle Attached

External counting over the anterior half of the globe requires that the tube face rest on the conjunctiva, not on the sclera. Unlike choroidal emissions, those from the conjunctiva travel to the tube chamber unimpeded by other tissue. Consequently, activity within the conjunctiva might contribute a high percentage of the total of emissions detected. The study to follow sought to examine two aspects of this problem: first, the influence of extraocular tissues on total ocular uptake and, second, the individual content of conjunctiva, muscle, and globe, when separately assayed.

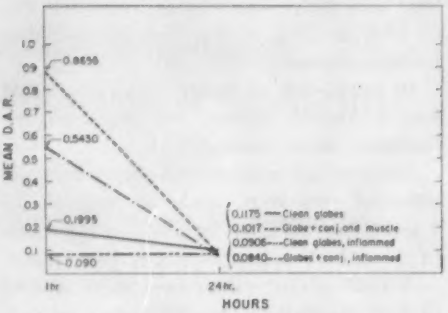

Fig. 1.—Radiophosphorus content of rabbit ocular tissue at 1 and 24 hours following intravenous injection of sodium radiophosphate, 50μc. Results are expressed as mean differential absorption ratio (see text); each of the eight ratios charted represents the mean of 12 rabbit eyes.

The procedures of Group I were repeated, with this difference: All conjunctiva and muscle anterior to the equator remained on the globes, as part of the specimen to be digested. The results are listed in Table 3 and depicted in Figure 1.

In comparison with Group I there resulted an approximate fourfold increase in mean D. A. R. at the one-hour interval. A rise is also reflected in per cent of dose figures. This elevation is out of proportion to the very small weight increase of the specimen that the retention of extraocular tissue brings about (about 2.0 mg.).

Six specimens each of conjunctiva, muscle, and globe were separately assayed at 1 and at 24 hours, to further test the implication of these results. Because dissection might cause diffusion of P^{32} between tissues, manipulations were minimized as far as possible. The rise of surface activity on the globes was less than 2% of total specimen activity, as determined by analysis of the collected saline wash fluid.

TABLE 2.—*Uptake of P^{32} in Normal Eyes*

	P^{32}		D.A.R.	
	μc/Gm., Range	% of Dose	Range	Mean
1 hr.	0.0020-0.0268	0.0040-0.0536	0.001-0.766	0.1995
24 hr.	0.0000-0.0083	0.0018-0.0166	0.035-0.263	0.1175

TABLE 3.—*P^{32} Uptake in Normal Eyes with Extraocular Tissues*

	P^{32}		D.A.R.	
	μc/Gm., Range	% of Dose	Range	Mean
1 hr.	0.0042-0.295	0.0084-0.590	0.136-2.950	0.8655
24 hr.	0.0006-0.0116	0.0012-0.0232	0.026-0.270	0.1017

TABLE 4.—*P^{32} Uptake of Dissected Tissues*

		P^{32}		D.A.R.	
		μc/Gm., Range	% of Dose, Range	Range	Mean
1 hr.	Conj.	0.0340-0.4640	0.0680-0.3214	1.26 -6.13	3.434
	Muscle	0.0324-0.0141	0.1048-0.2282	2.69 -4.76	3.157
	Globe	0.0015-0.0068	0.0030-0.136	0.060-0.272	0.123
24 hr.	Conj.	0.0534-0.202	0.1068-0.404	1.78 -7.22	3.297
	Muscle	0.0423-0.1710	0.0866-0.3420	1.41 -6.11	2.755
	Globe	0.0017-0.0026	0.0034-0.0052	0.061-0.087	0.0765

The 1- and 24-hour values for dissected tissues are presented in Table 4.

The data concerning mean D. A. R. values are charted in Figure 2. The specific uptake of radiophosphorus by conjunctiva and muscle exceeded that of cleaned globes at both the 1- and 24-hour intervals.

Between 0.068% and 0.928% of the 50μc dose was found in conjunctiva at one hour, and slightly less than this was found in muscle. Expressed as mean D. A. R., the lowest value for these tissues was 25 and 45 times, respectively, that of the cleaned globe at 1 and at 24 hours.

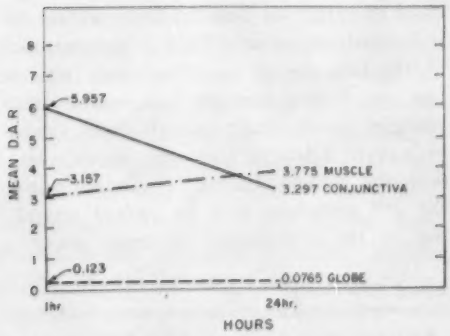

Fig. 2.—Radiophosphorus content of rabbit conjunctiva, muscle, and globe separately assayed at 1 and at 24 hours following intravenous injection of sodium radiophosphate, 50μc. Results are expressed as mean differential absorption ratio (see text); each of the six ratios charted represents the mean of six rabbit eyes.

Differential Uptake of Inflamed Globe

Interest was now directed to the effect that inflammation might have on ocular uptake of P^{32}. Bettman [8] has reported a great increase after the injection of turpentine into a single animal eye. The following studies were done to reproduce this effect and if possible to differentiate the role of ocular inflammation from that of conjunctival inflammation in promoting local uptake of radiophosphorus.

The anterior chamber was evacuated in 24 rabbit eyes and 0.2 ml.[30] of turpentine was injected intracameraly. The onset of an inflammatory response was prompt and severe. Fifty microcurie doses of P^{32} were injected intravenously after an interval of 15 minutes. Twelve eyes were enucleated at 1 and at 24 hours, and all extraocular tissues were removed. Table 5 contains the results of tissue assay in this group of eyes; mean D. A. R. values appear in Figure 1.

Needless to state, these low figures were an unexpected result. Despite the visible inflammation within all eyes, no single instance of increased radiophosphorus uptake occurred. Differences between 1- and 24-hour values were of the order found in normal eyes, studied at corresponding intervals (Group I).

In order to assess the role of extraocular inflammation, an experiment was done on

TABLE 5.—*P^{32} Uptake of Inflamed Globe*

	P^{32}		D.A.R.	
	μc/Gm., Range	% of Dose	Range	Mean
1 hr.	0.0004-0.0051	0.006 -0.0102	0.035 -0.205	0.0909
24 hr.	0.0013-0.0071	0.0026-0.0142	0.0064-0.229	0.0905

eyes subjected to a subconjunctival injection of turpentine (0.5 ml.). Without exception, the chemosis and injection were severe and persisted for several days. Intravenous sodium radiophosphate injection (50μc) followed in 15 minutes. All extraocular tissues anterior to the globe equator were retained on enucleated specimens, as in Group II.

The results are presented in Table 6; 1- and 24-hour mean D. A. R. values appear also in Figure 1.

At the one-hour interval extraocular inflammation did not evoke a rise of P^{32} above the resting level previously established (Table 3). Once more, retention of these external tissues (inflamed or not) caused or was accompanied by a marked increase of the one-hour P^{32} content.

At 24 hours the P^{32} content was no greater than that found in normal globes without inflammation (Tables 2 and 3). In this connection it is worthy of notice that regardless of inflammation or external tissue retention the mean D. A. R. value at 24 hours differed very little throughout these studies (0.0765 to 0.1175).

Per Cent Difference P^{32} Uptake Between Eyes of Same Animal

Most external counting techniques require that a comparison be made between the normal and the suspect eyes of a patient. This assumes that the disparity of isotope content which occurs naturally between paired organs is less than that which a tumor might evoke.

The foregoing experiments were designed to permit a limited comparison of P^{32} content between paired eyes.

In all there were 26 instances of bilateral enucleation. Twelve of these pairs were inflamed eyes (six intraocular, six conjunctival), and fourteen were not (six clean, eight with conjunctiva).

The mean D. A. R. difference in all pairs was 46%; the range of D. A. R. per cent differences for inflamed eyes was 6.1 to 60, and for uninflamed eyes it was 0.5 to 80.

Absorption of Radiophosphorus by Ocular Tissue

Any consideration of radiophosphorus detection must take into account, first, the nature of the emitted energy and, second, its absorption by overlying tissue.

Since it emits only beta radiations, P^{32} must exhibit wide differences of energy (and therefore of penetrability) among its individual emissions. This is an example of the beta energy spectrum, and from it one may deduce that any beta source emits energies whose range extends from almost zero up to a definite maximum which varies with the isotope studied.[14,15] Consequently, the P^{32} emissions may be plotted according to the distribution of their energies

TABLE 6.—*P^{32} Uptake of Inflamed Extraocular Tissue*

	P^{32}		D.A.R.	
	μc/Gm., Range	% of Dose	Range	Mean
1 hr.	0.0002-0.0234	0.0004-0.0468	0.011-0.936	0.5430
24 hr.	0.0010-0.0090	0.0020-0.0180	0.024-0.210	0.0840

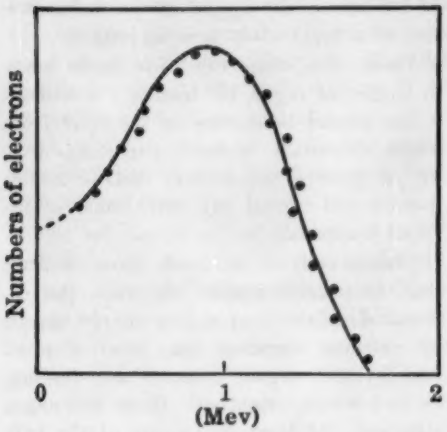

Fig. 3.—Beta energy spectrum of radioactive phosphorus (P^{32}).

(Fig. 3). Such a plot reveals that the highest energy for P^{32} is 1.7 mev but that the number of these maximally penetrating emissions is very small. The frequently repeated figure for tissue penetration of 8 mm. refers only to these 1.7 mev emissions and is too high a value for the average P^{32} emission energy, which is reported between 0.685 and 0.70 mev.[19-21]

An idea of the magnitude of ocular tissue absorption can be gained from this simple experiment: Three disks of human sclera were excised from a freshly enucleated eye; each was of 1 sq. cm. area. The disks were obtained from three separate areas of the globe; namely, adjacent to temporal limbus, beneath superior rectus insertion, and at the posterior pole. They were weighed and then placed in succession over the mouth of a narrow plastic cup containing 0.110μc of P^{32}. The total activity of P^{32} used here corresponded to that found in the first human tumor specimen described earlier in this report; the scleral disks were taken from this same eye. The scleral densities (mg/cm.^{2}) and their effects on counting results are shown in Figure 4. The over-all reduction of detectable radiation by scleral disks equalled about 66% of the counts per minute detected above the uncovered source.

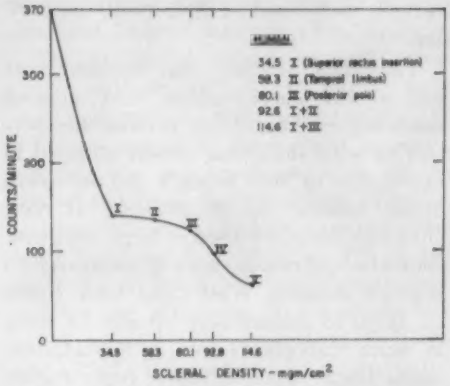

Fig. 4.—This chart illustrates the reduction of recorded counts per minute which follows interposition of varying scleral thicknesses between a Geiger tube and a 0.110μc P^{32} source. The counting geometry factor was 9.0% (see text).

Comment

The evidence upon which the reputation of tumor detection by P^{32} counting must rest is not all in. However, one thing about it is already reasonably clear: Conclusions which support the validity of an external counting technique appear to rest, to a great extent, upon several broad assumptions. Expressed in their simplest form these are the following:

1. Enough radiophosphorus enters the globe to assure accurate counting under clinical conditions, i.e., brief external Geiger probe counting.

2. Extraocular tissue covering the eye does not attract sufficient radiophosphorus to obscure emissions arising within the globe proper.

3. Scleral absorption does not significantly retard transmission of P^{32} emissions from the choroid to the counting tube.

4. The natural difference in P^{32} uptake between paired organs does not exceed that which occurs between a normal eye and a tumor-bearing one.

5. Ocular inflammation causes increased P^{32} uptake, but this is less than the uptake caused by intraocular tumor.

Whatever the reasons, none of these assumptions has been proven substantially

correct; each could be dangerously misleading.

Theoretical as they may appear, these and similar considerations have aroused much interest here chiefly because they pertain to some disturbing results obtained in our studies of both primary and metastatic ocular tumors. As an example, we have cited two instances wherein large malignant choroidal melanomas were associated with negative counting results and were found on assay to contain only 10 and 13 times as much radiophosphorus as the adjacent ocular tissue. Such a relative concentration is of the order found in primary brain tumor, and external counting results (I^{131}) there indicate that it is not an easily detected one.

With such low uptake in the ocular situation, the opportunity for misdiagnosis using the hand-positioned probe is remarkably good; any added limitations such as scleral absorption, inconstant geometry, or a short (one minute) counting time should further limit the reliability of such methods.

Much more desirable, when one is dealing with small tumors, would be the uptake ratio found with I^{131} in cases of thyroid malignancy (1000-10,000), but this is not possible with P^{32}.

Prominent among the reasons for our disenchantment with the external Geiger counting technique has been the poor performance of the cured posterior pole Geiger tube [10] (even when in direct contact with perforating malignant tissue; as in Case 1).

In ascribing reasons for the low tumor uptake cited one hesitates to assume that malignant melanomas normally behave this way. Their rapid growth implies high mitotic activity, and this, says Marshak [23,24] draws radiophosphorus into the nucleoprotein of tumor in greater than usual amounts. It is of interest, however, that his reports do not deal with melanoma; nor, for that matter, do most other basic studies cited to support use of P^{32} for ocular melanoma detection.[9,13,26] This problem, the uptake of P^{32} specifically by melanoma, is the subject of a basic study now in progress.

There is obvious need for tissue assay in studies of organ P^{32} uptake, for without it one cannot be certain of the level from which externally counted emissions arise or, of greater importance, that all malignancies will exceed any other cause of increased uptake.

Theoretically it is much more difficult than is usually realized to trace the internal distribution of a beta energy source by external counting done over a small multilayered organ. There are limiting factors which arise both from the organ structure and from the nature of the beta emission itself, and several aspects of this problem have been considered in the foregoing study. Of greatest significance are those results which indicate that the specific ocular uptake of P^{32} is very low and is, at least in the rabbit eye, significantly less than that of either conjunctiva or muscle.

In theory this low ocular uptake might be explained by two factors: the amount of blood-borne isotope brought to the eye (a function of ocular blood volume and flow rate) and the per cent of delivered isotope that is retained therein (related to the intensity of mitosis [tumor] or phosphorylation reactions [retina]). If it is true that the estimated ocular blood volume is only 0.2 ml.[30] and that most choroidal tumors are relatively small, it follows that the position of intraocular melanoma is a disadvantageous one.

A further reason for low ocular uptake is suggested by Palm,[29] whose work shows the rate of radiophosphate exchange between blood and aqueous to be much lower than that expected when simple phosphate ion exchange occurs in other body tissues. In all probability such a delay is crucial in view of the known rapid fall of plasma P^{32} level after intravenous injection (98% at two hours).[28]

Certain additional basic findings demonstrated in this study will require more statistical support. These are, first, the

wide differences in uptake noted between eyes of the same animal and, second, the role of scleral absorption on choroidal emissions. Should the 46% (mean D. A. R.) difference between eyes of a pair prove valid, there is need to revise the upper normal figure of 30% (as Palin and Tudway suggest [25]).

The relation of scleral absorption to P^{32} beta emission deserves further study. If, in fact, choroidal emissions are two-thirds absorbed by sclera and are numerically exceeded by conjunctival sources, the validity of external counting is suspect, especially at the one-hour interval.

Taken singly or together, the foregoing limitations indicate a need for further justification of present dosage and counting methods. If, as noted here, the contribution of current methods to the detection of choroidal tumor does not outweigh that of routine clinical examination, the method might best be set aside until improved.

Summary

With data obtained from tissue assay, the P^{32} differential absorption ratio (D. A. R.) and per cent of dose values were calculated for two eyes each containing a large malignant melanoma. The tumors contained only 10 and 13 times the radioactivity of adjacent posterior segment tissue. The curved Geiger counting probe [18] in these and other primary and metastatic posterior tumors did not indicate any increased P^{32} concentration in the tumor area.

The mean differential absorption ratio obtained for a group of cleaned rabbit eyes (conjunctiva and muscle removed) was only 20% of the whole body average during the first 24 hours. Analysis of a second group of eyes on which extraocular tissue was retained indicated a fourfold increase of radiophosphate uptake at 1 hour but not at 24.

When they were dissected and separately analyzed, however, the specific uptake of conjunctiva and muscle exceeded that of the globe by a factor of about 25 at both one- and 24-hour intervals (Fig. 2).

The effects of intraocular and extraocular inflammation on P^{32} uptake were separately studied. Intracameral turpentine injections caused a severe uveal response, but this was not accompanied by an increased uptake of radiophosphate (Fig. 1). Subconjunctival turpentine injection also failed to evoke an increase of P^{32} uptake above levels found for noninflamed eyes.

When the difference in P^{32} uptake between opposite eyes was calculated in 26 animals (13 inflamed and 13 normal), the average difference in mean D. A. R. was 46%, and in some noninflamed pairs this figure exceeded 60%.

Human sclera of three thicknesses absorbed about 66% of the emissions of a subjacent 0.008μc P^{32} source.

Discussion of these results deals with the need for further justification of present dosage and external counting methods.

Ophthalmology Branch, National Institute of Neurological Diseases and Blindness.

REFERENCES

1. Scarney, H. D., and Crossin, R. J.: An Interesting Case of Melanosarcoma, Kresge Eye Inst. Bull. 3:53-54 (Nov.) 1951.

2. Thomas, C. I.; Krohmer, J. S.; Storaasli, J. P., and Friedell, H. L.: Detection of Intraocular Tumors by the Use of Radioactive Phosphorus, Am. J. Ophth. 38:93-99 (July, Pt. II) 1954.

3. Dunphy, E. B., and Selverstone, B.: Uptake of Radioactive Phosphorus by Normal and Neoplastic Ocular Tissues, Am. J. Ophth. 36:774-776 (June) 1953.

4. Dunphy, E. B.; Dreisler, K. K.; Cadigan, J. B., and Sweet, W.: The Uptake of Radioactive Phosphorus by Intraocular Neoplasms, Am. J. Ophth. 37:45-54 (Jan.) 1954.

5. Bettman, J. W., and Fellows, V.: A Scintillation Counter for the Diagnosis of Intraocular Melanomas, Am. J. Ophth. 39:170-177 (Feb., Pt. II) 1955.

6. Eisenberg, I. J.; Leopold, I. H., and Sklaroff, D.: Use of Radioactive Phosphorus in Detection of Intraocular Neoplasms, A. M. A. Arch. Ophth. 51:633-641 (May) 1954.

7. Eisenberg, I. J.; Terner, I. S.; and Leopold, I. H.: Use of P^{32} as an Aid in Diagnosis of Intraocular Neoplasms: Further Observations, A. M. A. Arch. Ophth. 52:741-750 (Nov.) 1954.

8. Bettman, J. W., and Fellows, V.: Radioactive Phosphorus as a Diagnostic Aid in Ophthalmology, A. M. A. Arch. Ophth. 51:171-179 (Feb.) 1954.

9. Low-Beer, B. V. A.: Surface Measurements of Radioactive Phosphorus in Breast Tumors as a Possible Diagnostic Method, Science 104:399 (Oct. 25) 1946.

10. Thomas, C. I.; Krohmer, J. S., and Storaasli, J. P.: Geiger Counter Probe for Diagnosis and Localization of Posterior Intraocular Tumors, A. M. A. Arch. Ophth. 52:413-414 (Sept.) 1954.

11. Dunphy, E. B.; Dreisler, K. K.; Cadigan, J. B., and Sweet, W.: The Uptake of Radioactive Phosphorus by Intraocular Neoplasms, Tr. Am. Ophth. Soc. 51:345-370, 1953.

12. Owens, W. C.; King, H. J., and Wells, H. S.: Radioactive Phosphorus for the Detection of Intraocular Tumors, Am. J. Ophth. 41:507-513 (Mar.) 1956.

13. Selverstone, B.; Solomon, A. K., and Sweet, W. H.: Location of Brain Tumors by Means of Radioactive Phosphorus, J. A. M. A. 140:277-278 (May 21) 1949.

14. Glasstone, S.: Source Book on Atomic Energy, New York, D. Van Nostrand Company, Inc., 1950, p. 162.

15. Lapp, R. E., and Andrews, H. L.: Nuclear Radiation Physics, Ed. 2, New York, Prentice-Hall, Inc., 1954, p. 177.

16. Marinelli, L. D., and Kenney, J. M.: The Absorption of Radiophosphorus in Irradiated and Non-Irradicated Mice, Radiology 27:691-697 (Dec.) 1941.

17. Burtt, B.: Standardization and Use of RAE for Absolute Beta Counting, in Conference on Absolute Beta Counting, Preliminary Report No. 8, National Research Council, Oct., 1950, pp. 1-7.

18. Snedecor, G. W.: Statistical Methods, Ames, Iowa, Iowa State College Press, 1946, p. 28.

19. Atomic Energy Commission, Nuclear Science Abstracts (No. 24B), 6:14, 1952.

20. Nuclear Data, Circular No. 499, National Bureau of Standards, 1950, p. 27.

21. Glasser, O.; Quimby, E. H.; Taylor, L. S., and Weatherwax, J. L.: Physical Foundations of Radiology, Ed. 2, New York, Paul B. Hoeber, Inc., 1952, p. 391.

22. Pollard, E., and Davidson, W. L., Jr.: Applied Nuclear Physics, New York, John Wiley & Sons, Inc., 1942, p. 108.

23. Marshak, A.: Uptake of Radioactive Phosphorus by Nuclei of Liver and Tumors, Science 92:460-461, (Nov. 15) 1940.

24. Marshak, A.: P^{32} Uptake by Nuclei, J. Gen. Physiol. 25:275-291 (Nov.) 1941.

25. Palin, A., and Tudway, R. C.: The Use of Radioactive Isotopes in the Diagnosis of Intra-Ocular Malignancy, Tr. Ophth. Soc. U. Kingdom 75:281-299, 1955.

26. Kenney, J. M.; Marinelli, L. D., and Woodard, H. Q.: Tracer Studies with Radioactive Phosphorus in Malignant Neoplastic Disease, Radiology 37:683-687 (Dec.) 1941.

27. Thomas, C. I.; Krohmer, J. S., and Storaasli, J. P.: Detection of Intraocular Tumors with Radioactive Phosphorus: A Preliminary Report with Special Reference to Differentiation of the Cause of Retinal Separation, A. M. A. Arch. Ophth. 47:276-286 (March) 1952.

28. Hevesy, G.: Application of Radioactive Indicators in Biology, Ann. Rev. Biochem. 9:641-662, 1940.

29. Palm, E.: On the Phosphate Exchange Between the Blood and the Eye, Acta Ophth., Supp. 32, p. 106, 1948.

30. Becker, B., and Friedenwald, J. S.: Clinical Aqueous Outflow, A. M. A. Arch. Ophth. 50:557-571 (Nov.) 1953.

Sponge Attachment for Epiphora

P. THOMAS MANCHESTER Jr., M.D., Atlanta

A simple method for relieving epiphora is the attachment of an absorbent sponge to the patient's glasses so that it lightly touches the inner canthus. This should be beneficial for any type of tearing except in those cases which are due to inflammation. In patients with "crocodile tears," facial palsy, or contracture of the lacrimal punctum a sponge may be useful.

An interesting circumstance occurred in one patient with chronic epiphora who noticed that before use of the sponge her eyelids and conjunctivae were irritated from constant rubbing with a handkerchief. Use of the sponge allowed the irritation to subside, and there was less tear production than before.

A small wire loop can be used to hold the sponge, and this is then bradded or soldered to the glasses just behind the nose piece.* Any optician can attach the loop in a few minutes. Figures 1, 2 and 3 demonstrate the wire in use.

Received for publication Dec. 10, 1956.

* Made by Mr. E. F. Rudisill, Ballards Opticians, 478 Peachtree St., Atlanta.

Fig. 1.—Wire loop attachment, posterior view.

Fig. 2.—Wire loop attachment, anterior view.

Most household polyester sponges become rather stiff when they dry out, making them unsuitable for pressing against the inner canthus of the eye. There is one sponge, however, which is very absorbent and which remains soft always.† It can be obtained in flesh color and is easily cut and rounded to the desired shape with scissors. A small notch in the center of the sponge will allow it to remain in the metal ring. Patients should be directed to wash the sponge in soap and water at regular intervals.

478 Peachtree St., N. E. (3).

† O-CEL-O Soap Dish, General Mills Inc., Buffalo, N. Y.

Fig. 3.—Sponge in use.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted, and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest, and be accompanied with photographs whenever possible.

Severe Membranous Conjunctivitis with Recovery

Membranous and pseudomembranous conjunctivitis has been reported occurring with a wide variety of organisms as the exciting cause. The β-hemolytic Streptococcus is one of the organisms often implicated. The following case is noteworthy because of severe corneal involvement and remarkable recovery.

Report of Case

A 12-year-old white boy was admitted to the Massachusetts Eye and Ear Infirmary on May 7, 1953, with the history that four days previously he had awakened with a slight sore throat and a red, swollen left eye. There had been a slight discharge from the eye, and his vision was blurry from the onset. His eye became less red in a day or so, and the discharge decreased. There was no improvement in vision.

On admission the right eye was normal, with a vision of 20/30. The vision in the left eye was accurate light projection. Moderate edema of both lids was present, and the entire palpebral and bulbar conjunctiva was coated with a thick dry gray-white membrane. The cornea was insensitive and

Received for publication Dec. 3, 1956.

From the Massachusetts Eye and Ear Infirmary, Boston.

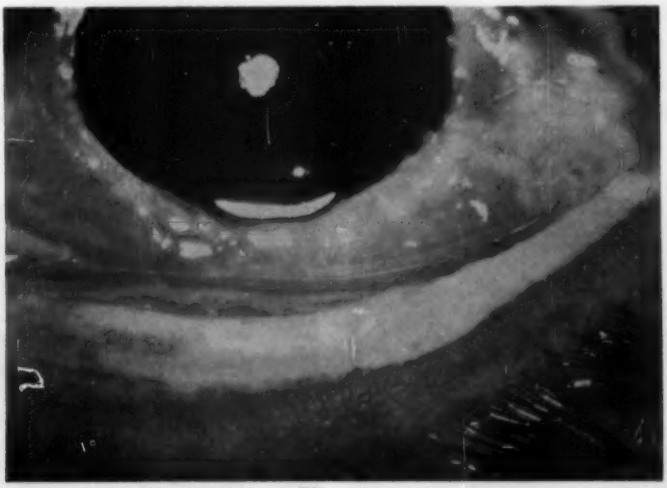

Figure 1

of marked ground glass appearance (Fig. 1). An aqueous flare was dimly apparent, and there seemed to be a small sheet-like membrane in the upper nasal portion of the anterior chamber and across the lower half of the pupil. The left pupil was smaller than the right, but it reacted to light. Movements of the globe were slightly restricted in all directions. The membranes of the palpebral conjunctiva could be peeled off easily in one piece, with slight bleeding only. On the globe the membrane was densely adherent and could be removed only in small fragments, with marked discomfort and bleeding. There was no preauricular adenopathy.

General physical examination disclosed that both nasal cavities were filled with yellow pus and that white patches were present on the septum and posterolateral wall of the left cavity. Small follicular patches were present on the posterior pharyngeal wall and in the right tonsillar fossa. The temperature was 99 F.

Microscopic examination of the membrane showed it to contain many polymorphonuclear leukocytes and Gram-positive diplococci. Cultures grew pure β-hemolytic streptococci. Cultures on Klebs-Loeffler medium were negative. Urinalysis was negative. There were 14,900 WBC, with a normal differential count.

Treatment with systemic penicillin and sulfisoxazole (Gantrisin) and local penicillin drops and ointment, bacitracin drops, and atropine was begun on admission. Two days later the membranes were as extensive as previously and at the limbus the superficial corneal layers were becoming necrotic (Fig. 2) despite the now negative cultures. Streptokinase-streptodornase (Varidase) ointment was added to the local treatment.

Over the next 10 days the membranes gradually ceased to re-form over the conjunctiva when removed, but the superficial cornea became increasingly necrotic. By May 20, 1953, only a small residual membrane was present at the limbus and the entire conjunctiva showed many new vessel buds. The cornea showed a definite superficial loss of substance throughout and was densely infiltrated except for a small central area, through which, however, the anterior chamber was not visible (Fig. 3).

The patient was discharged from the hospital on May 22, 1953, after two courses of intravenously administered typhoid vaccine, which seemed to produce no improvement. His visual acuity was then accurate light projection. He was instructed to use 1%

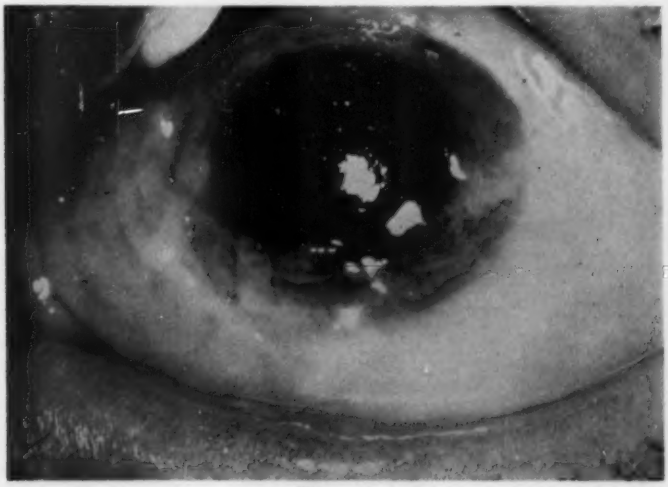

Figure 2

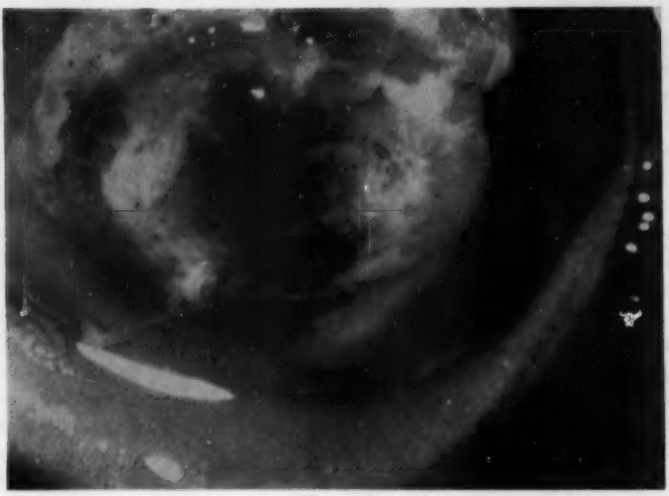

Figure 3

atropine, 0.5% cortisone, and bacitracin drops at home.

After discharge, improvement in the cornea was slow but steady. Convalescence was complicated by a bout of secondary glaucoma, which subsided permanently after about six weeks and left no residual field defect. Vascularization of the cornea accompanied disappearance of the infiltrate and smoothing of the surface. It was estimated that between one-quarter and one-third of the corneal substance had been lost.

Eight months after the onset of the infection the visual acuity had improved to 20/50 and the cornea had scattered areas of band keratopathy with continued slight surface irregularity. All treatment was then discontinued.

One year after onset the conjunctiva was unremarkable. The cornea appeared lustrous and smooth, though thinned (Fig. 4). Ghost

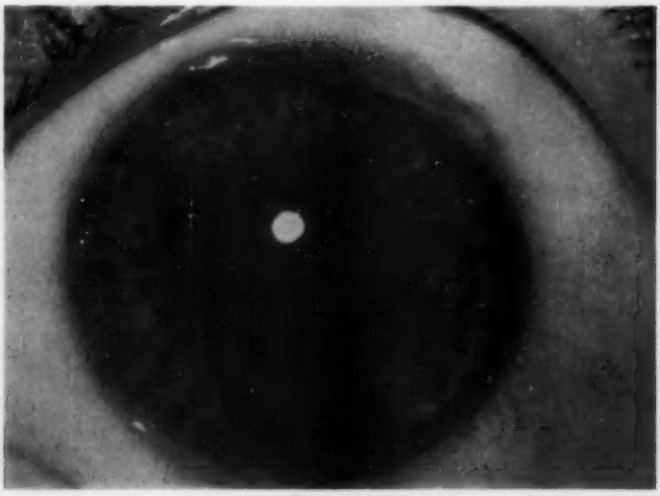

Figure 4

vessels were apparent in the midstroma. Visual acuity was 20/40. The pupil was eccentric, presumably because of a uveitis which accompanied the acute infection.

When he was last seen, two years after the initial infection, there had been no change in the patient's visual acuity or the physical status of his eye.

Summary

A case of membranous conjunctivitis with necrosis of the cornea and the return of useful vision is reported.

Photographs were made by Dr. David D. Donaldson, of the Howe Laboratory of Ophthalmology, Boston.

ROBERT J. HERM, M.D.
740 Main St., Waltham 54, Mass.

Annual Reviews

Diseases of the Retina and Optic Nerve

ROBERT W. HOLLENHORST, M.D., Rochester, Minn.

As in other years, the literature on diseases of the retina and optic nerve was extremely voluminous in 1956. Most of the papers were concerned with further work on retrolental fibroplasia and the surgical repair of retinal detachment. Most of this subject matter was discussed in one or more papers. I have tried to include only those articles that I considered of particular interest published since the previous annual review, written by Wagener.[1]

Retrolental Fibroplasia

There seems little question that the efforts of the many workers doing research in this field have been richly rewarded. Although the mechanism of action of oxygen in producing the changes of retrolental fibroplasia has not yet been definitely ascertained, it seems clear that the reduced incidence of retrolental fibroplasia is due to curtailment of the use of oxygen for premature babies. Duke-Elder and associates[2] reported on 1095 premature babies who weighed less than 4 lb. (1800 gm.) and of whom 84 (7.7%) had retinopathy. Of these, 39 became normal, but the remaining 45 (53%) had severe loss of vision in one or both eyes (4.1% of the 1095 babies). During pregnancy, 115 mothers bled; 17 (14.8%) of their babies had retinopathy. The 976 mothers who did not bleed had only 67 (6.9%) babies with retinopathy. The incidence of retinopathy was greatest when oxygen was used. Restriction did not increase the mortality rate. Among 344 babies for whom oxygen was not used, none had retinopathy. Of the 581 given oxygen for less than 5 days, 2 (0.3%) had retinopathy; the 25 given oxygen for 40 days or more had a 64% incidence of retinopathy. Healing of the retinopathy was not influenced by the length of time the infant was kept in oxygen or by the mode of withdrawal from oxygen. The time of onset of retinopathy varied between 27 and 56 days, being longer the more premature the baby. Boyd and Hirst[3] measured the incidence of retinopathy among 6926 infants born in England and Wales in 1951. It appeared in 127 (1.83%) of those weighing less than 4 lb. 6 oz. (1985 gm.); in 2.8% of those weighing less than 4 lb. (1800 gm.), and in 15.3% of those weighing less than 2 lb. 4 oz. (1020 gm.). No cases of the disease appeared among 797 premature infants born at home and not transferred to a hospital. Guy, Lanman, and Dancis[4] reported on 81 premature infants given little oxygen. None developed cicatricial retrolental fibroplasia, and only three (4%) had mild vascular-stage lesions. These lesions later healed. This is in contrast to the control group of 36 infants who received large amounts of oxygen and among whom there were vascular lesions in 61% and cicatricial lesions in 22%.

Kinsey, Jacobus, and Hemphill[5] reviewed the cooperative study conducted in 18 hospitals on 786 infants, of whom 53 received routine oxygen administration and 533 a curtailed supply. The incidence of active

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Section of Ophthalmology, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

retrolental fibroplasia in the routine-oxygen group was twice that occurring in the curtailed-oxygen group, while the incidence of the cicatricial grade of the disease was three and a half times greater. The authors observed that even among the infants on curtailed oxygen there was an incidence of 31.3% active retrolental fibroplasia in single births and of 41.7% in multiple births. There was an incidence of cicatricial retrolental fibroplasia in 4.7% of single births and in 13.9% of multiple births. These figures contrasted with 70.2% and 83.3%, respectively, of active retrolental fibroplasia and 17.0% and 66.7% of cicatricial retrolental fibroplasia among the routine-oxygen group. Even though oxygen unquestionably plays an extremely important role, the administration of it therefore is obviously not the complete answer in the pathogenesis. The symposium conducted at the International Congress by Ashton, Gordon, Szewczyk, Bedrossian, Carmichael, Ritter, and Locke [6] discussed the relative importance of hyperoxia, hypoxia, and hyperoxic hypoxia. It is possible that the newborn infant has a greater tolerance for anoxia than has the adult. It is also possible that a state of relative anoxia may be normal and quite harmless to the premature baby.[7] Two of the six patients reported by Hollenhorst [8] may have developed retrolental fibroplasia because of severe anoxia. One infant was toxemic with multiple abscesses. The other was born to a mother who died nine days later of advanced cardiac disease and massive cerebral hemorrhage. Both received a curtailed supply of oxygen.

Castrén [9] wrote a monograph on the subject of retrolental fibroplasia, reporting the examination of 723 persons born between the years 1937 and 1955, of whom two-thirds were premature and the other third full-term. The average age of each group was about 9 years. No differences were noted as to refraction, heterophoria, and color blindness. Six per cent of infants who weighed less than 2250 gm. at birth developed strabismus. Only 2.3% in the full-term group had this defect. Amblyopia occurred in 4% of 480 premature infants and in only 1.4% of full-term children. Twenty-six children had retrolental fibroplasia. Of these, three weighed more than 2500 gm. at birth, but 20 weighed less than 1750 gm. Twenty of the twenty-six had received oxygen therapy averaging 40 days. None of the 475 premature infants who had been selected for this study by birth weight alone and who had not been treated in modern oxygen incubators had the disease. Eight patients with retrolental fibroplasia of nine who received blood transfusions had the severest form of the disease.

Greenhouse and Szewczyk [10] described a child with retrolental fibroplasia who had also a large hemangioma of the right side of the face. They discussed the somewhat higher occurrence of hemangioma among children with retrolental fibroplasia (14.3% of 26) than among those without retrolental fibroplasia (7.9% of 256). Development of hemangioma seems unrelated to oxygen administration.

Melanowski and Kobuszowski [11] performed a pathologic examination of two eyes removed because of retrolental fibroplasia and hydrophthalmos. These eyes showed aplasia of Schlemm's canal, degeneration of the corneoscleral trabeculae, and proliferation of the connective tissue with formation of telangiectatic capillaries. It was suggested that this was all part of a generalized vascular dysplasia.

Experimental Studies.—Hellström has continued his extensive investigation of the effect of oxygen on the retina of experimental animals and has recently published a monograph [12] based on the 10 papers he has written on this subject. The first three of these were reviewed in this section last year. His fourth to seventh papers have been published.[13-16] The last three are to be published and concern intense and prolonged oxygen exposure, the behavior of succinic dehydrogenase in the retina, and in vitro metabolism of the retina. He con-

cluded on the basis of his own and other investigations as follows:

Oxygen causes an inhibition of retinal vascularization, and constriction and obliteration of already developed retinal vessels. Revascularization is frequently excessive and abnormal with proliferating vessels of the nerve fiber layer budding into the vitreous body. This vasoproliferative phase occurs chiefly on transfer to air, but minor proliferations may occur in oxygen, especially when lower concentrations are used. The vascular changes occur only in eyes with incomplete vascularization. The proliferative changes may be delayed through a process of slow weaning, but the other pathologic changes of the eye are not influenced. Among factors influencing both normal and pathologic vascularization is the state of nutrition.

Hellström found further that prolonged oxygen exposure causes atrophy of the inner layers of the retina. Oxygen does not seem to cause an enzyme inhibition or a primary metabolic disturbance, and general hypoxia seems to play no role.

In an effort to try to clarify the relation of hypoxia to retrolental fibroplasia, Habegger, Philbrook, Curley, and Ingalls [17] subjected mice to daily hypoxic stresses. The pathologic changes produced in the eyes were remarkably similar to those produced by hyperoxia and came on much more rapidly. Abnormal congestion, persistence, and proliferation of the branches of the hyaloid artery system could be demonstrated after either hypoxia or hyperoxia, if it was sufficiently severe and prolonged in the neonatal period. Michaelson [18] showed apparently convincing evidence that new-vessel formation is related to oxygen deficiency or to some diffusible factor which appears in the tissues. Newly budding vessels in the retina arise on the vitreous side of vessels and on the side of the vein away from adjacent arterioles; in the cornea, on the side of the vessel nearest the site of injury, and in fistulas, on the side of the vessel away from the aqueous. Mercier [19] gave chlorpromazine to 30 of 77 premature infants to try to prevent retrolental fibroplasia on the basis that guinea pigs were protected by this drug against pulmonary congestion at high oxygen concentration, but there was no difference in the incidence of retrolental fibroplasia in the two groups.

Kozuchowska [20] found retinal hemorrhages among 27% of 310 newborn infants within the first few hours after birth. Two-thirds of these hemorrhages were bilateral. Humblet, Cavrot, and Richard [21] found that such hemorrhages depended on the type of delivery, and that 10 mg. of vitamin K given to the mother twice daily during the last month of pregnancy diminished the incidence. McNeil [22] and Birge [23] emphasized the frequency of myopia among prematurely born children. The former found this true even when no oxygen had been used or retrolental fibroplasia had been noted. The latter found the myopia residual to retrolental fibroplasia to be severe but not progressive, and it was often associated with strabismus, nystagmus, or optic atrophy.

Retinopathy in Diabetes

Tassman [24] recently published a complete exposition of the various ocular manifestations of diabetes mellitus. It is not possible to abstract this article adequately, and it should be read in its entirety. Urrutia, Bitran, Bonnefoy, and Pinto [25] examined 433 diabetic patients and found 36% with diabetic retinopathy, only 6 of them with retinitis proliferans or glaucoma. In their opinion, retinopathy is related both to the severity and to the duration of the diabetes. Miratynska-Rusinowa and Lisiecka-Adamska [26] found 142 (19%) cases of retinopathy among 750 diabetic patients. This was unrelated to the duration of the disease; it was found mostly in subjects more than 40 years of age, and more frequently in those having severe than in those having mild diabetes. Four of their patients who had chronic pancreatitis without diabetes had a retinopathy of the diabetic type. Dollfus [27] examined 1300 diabetic patients, finding 681 (52.4%) with ocular complications, of which 569 (43.7%) were retinop-

athy. There were 89 cataracts, of which 35 were diabetic and the others senile, and 23 lesions of the nervous system (ocular muscle palsy or retrolbulbar neuritis). There was no case of lipemia retinalis. Of patients less than 45 years of age 70.5% were free of ocular complications, but all 35 patients with diabetic cataract were less than 50 years old. Only 25% of those who had had diabetes less than 7 years had retinopathy, but those with more than 15 years of diabetes had an incidence of 75% to 88%. Dollfus found retinopathy to be commoner in the presence of a renal lesion than in its absence.

Lundbaek [28] found 4% retinopathy among 246 patients with recently diagnosed diabetes. All were more than 40 years of age, and none had severe diabetes. Givner [29] examined 286 children with diabetes and found only 6 (1.5%) who had diabetic retinopathy. Among these six, two had albuminuria and two had cataracts. Both of the latter were 15 years of age. Givner called attention to the role of hypoglycemic reactions in producing retinopathy or vitreous hemorrhage and advised that the blood sugar of patients with so-called brittle diabetes be maintained at a level sufficiently high to prevent such reactions. He has found no medication of value for diabetic retinopathy. Kornerup [30] measured the visual acuity of unselected diabetic patients and found worse prognosis for those whose age of onset was later in life, worse for females, and worse when the blood pressure was elevated. Fischer [31] discovered 17 patients who had papilledema among 300 who had diabetes; the majority of these had nephropathy, and a few had increased intracranial pressure.

Pathologic Physiology.—Quiroz and Sauter [32] believe that alterations in the veins are capable of producing an arteriolar spasm which, if sustained, may give rise to structural changes of arteriolosclerosis. These may later cause the retinal changes of diabetic retinopathy. Volk [33] called attention to the pathologic differences between the retinal lesions of diabetes and those of intercapillary glomerulosclerosis. He postulated that the latter may be closely associated with arteriolosclerosis appearing both in the kidneys and in the retina of patients with Kimmelstiel-Wilson disease.

Kornerup [34] found that Göthlin's petechial index increases in diabetic patients with advancing age just as it does among nondiabetic persons. Of 376 patients with diabetes, 38.4% had diabetic retinopathy; the petechial index increased with the severity of retinopathy. Twenty-nine and five-tenths per cent had hypertension with retinal vascular disease; the index increased with the degree of retinal vascular change. Kornerup concluded that hypertension, diabetes, or both caused the increased petechial index. Results of therapy with rutin and allied substances were not convincing.

Lerman and Pogell [35] found a 15% increase in the α_2-globulin fraction of the blood serum in diabetics with retinopathy. There was no difference in the amounts of this fraction found in normal persons and in diabetic patients without retinopathy. These globulins are reported to contain large amounts of mucoprotein. Similar determinations on the serum of alloxan-diabetic rabbits revealed no change after four weeks. One week after administration of 8.3 mg. of cortisone daily, this globulin increased 17%, and after three weeks, 27%. The authors noted that, since this level of cortisone produces intercapillary glomerulosclerosis in rabbits, it appears that the increase in the α_2-globulin fraction occurs simultaneously with capillary lesion formation in human beings and rabbits.

Morone [36] reported that there was a correlation between retinal complications and high glucosamine levels in the serum of 44 patients with diabetes and that insulin favorably influenced the concentration of glucosamine. He also studied [37] the behavior of this substance in the vitreous mucoids of experimental diabetes and found a sim-

ilar parallel between vascular modifications and the behavior of these polysaccharides. Harris and Lerner [38] found that the majority of diabetic patients with retinopathy had an increased urinary excretion of the melanocyte-stimulating hormone of the pituitary; diabetic patients without retinopathy had a normal output. The excretion was likewise elevated among patients with retinitis pigmentosa, choroideremia, and bilateral enucleations.

De Conciliis [39] induced hypoglycemia in rabbits by insulin injections. In acute cases, the permeability of the blood-aqueous barrier was increased and the fundi showed dilated veins and hemorrhages. In chronic cases, these changes were even more evident and were accompanied by opacities of the lens, decreased retinal respiration, and vitreous hemorrhages. He attributed these changes to a mechanical factor (muscular contraction) and to a vasodilator action of insulin.

Therapy.—Fischer [40] reviewed the entire history of therapy of diabetic retinopathy; he concluded that at present the trend is toward prevention by good diabetic control. Lijó Paviá [41] reported rapid improvement of vision in a patient with severe retinopathy and macular degeneration when 3 intraorbital and 10 subconjunctival injections of 10 mg. of cortisone were given. Schimek [42] discussed five patients with retinopathy in whom surgical hypophysectomy had no effect on the impaired vision, except for one patient whose vision improved slightly in one eye and another patient whose vision improved in one eye and became worse in the other. Malins [43] reported on six patients who underwent adrenalectomy, with no more convincing results.

Hypertensive Disease

Elwyn [44] reviewed and discussed his concept of the clinical and pathologic changes found among patients with benign essential hypertension, with arteriospastic retinopathy, and with malignant hypertension. Birge [45] presented an outline of the ophthalmoscopic findings of hypertension and portrayed the various factors concerned in making a valid diagnosis. He also stressed the importance of the polycythemic syndrome in the production of retinal vascular occlusive disease. Sautter [46] discussed the pathology, clinical findings, and therapy of the various forms of arteriosclerosis which affect the retinal vessels, following Bell and Friedenwald in his classification. Weigelin [47] expressed the opinion that the Keith-Wagener system of classification of essential hypertension is deficient in not separating patients with retinal vascular involvement and retinal hemorrhage (but without soft exudate) into a separate group. He proposed that these be designated Group III of Keith-Wagener, and he felt that the present Groups III and IV should be Groups IV and V, respectively. He came to this conclusion through measuring the distribution frequency of various blood-pressure levels. Wagener,[48] in discussing the paper, agreed that such patients do seem to present certain features in common.

Lijó Paviá [49] called attention to the value of knowing the ratio of retinal to brachial diastolic blood pressures. A high relative retinal pressure (50% or more than the brachial) portends a poor prognosis for the hypertension. Miller and Audoueineix [50] noted that 86% of patients who have malignant (Keith-Wagener Group IV) hypertension have a retinobrachial ratio higher than 50%, while 72% of patients with benign hypertension have a ratio less than this figure. The high ratios occur in an even greater percentage among patients who have retinopathy of glomerulonephritis.

Kunitomo and associates [51] examined 237 hypertensive and 457 normotensive patients with the ophthalmoscope and slit lamp, examining the conjunctival, ciliary, and retinal vessels of each subject. In benign hypertension the more marked irregularity in the vascular lumina was found in the conjunctival and ciliary vessels, but in malignant hypertension the severer changes were

in the fundi. Normotensive patients had normal blood vessels in all locations.

Sasamoto[52] believes the acetylcholine test to be valuable in hypertensives. He found that the intensity and duration of the reaction were reduced parallel to the fundus changes and to elevation of the diastolic blood pressure. The reaction was reduced most in the Group IV patients, in whom the duration was less than 60 minutes, compared with the normal 90 minutes.

Winter, Laron, and Michaelson[53] presented an interesting case of thallium poisoning in a 9-year-old boy in whom the retinal arterioles became extremely narrowed. The child had severe but transient hypertension. Even after the blood pressure returned to normal, the retinal arterioles remained narrow. The authors postulate that thallium may have a direct effect on the smooth muscle of the small blood vessels and that this effect may have produced the hypertension. Renal studies showed no abnormalities of a degree sufficient to account for the hypertension.

Hagans, Brust, and Ferris[54] studied patients with malignant hypertension and found that groups of patients with Grade 3 and Grade 4 fundi had a similar mortality rate (87% and 88%, respectively). However, the Grade 3 patients survived much longer (18.8 months) than the Grade 4 (3.3 months), considering only patients who did not have uremia initially. These authors studied 64 patients with untreated malignant hypertension over an average period of four years.

Kirby and Hollenhorst[55] reported on two interesting patients who had asymmetric hypertensive changes in the two fundi. The retina on the side ipsilateral to the ligated internal carotid artery had mild or absent hypertensive arteriolar changes, while the contralateral eye had changes commensurate with the degree of systemic hypertension. This is presented as evidence that retinal hypertensive vascular changes may be merely local manifestations in response to increase of pressure in the ophthalmic artery. The ophthalmodynamometer indicated a notably lower retinal artery pressure on the side of the carotid ligation.

Treatment of Hypertension.—Newborg and Kempner[56] analyzed 177 cases of hypertensive disease with papilledema and treated 126 with the rice diet. On the basis of their findings they stated:

> Since most cases of malignant hypertension are preceded by known "benign" hypertensive vascular disease, malignant hypertension can now be regarded as a preventable condition. Hypertensive disease, no matter how mild the symptoms, should be treated immediately and vigorously as soon as the diagnosis has been established.

Volkova[57] advocated 0.25% procaine (Novocain) hydrochloride injected into the retrobulbar tissues of patients with fundus changes of hypertension. He treated 31 patients in this way two or three times at 10-day intervals. He stated that the best results were obtained among patients who had sustained recent occlusions of the central retinal artery. In the late stages of hypertension the injection was ineffective.

Retinal Vascular Occlusions

Turner and Bowers,[58] in an editorial, presented an interesting summary of the role of the minute blood vessels in various diseases such as diabetes, thrombotic thrombocytopenic purpura, scurvy, and hypertension. They showed that fatty cysts produced by alcoholic cirrhosis may actually rupture into the blood vascular channels and produce emboli, thus perhaps accounting for the massive cotton-wool patches sometimes found in patients with cirrhosis. They called attention to the role of arterial spasm, focal ischemia, and increased permeability of brain capillaries as responsible for hypertensive encephalopathy. They noted that lipid material from an atheromatous ulcer might block small vessels and might actually be responsible for a renal artery occlusion and cause malignant hypertension. Sickle cells may occlude vessels. Fibrinogen thrown into the circulation, as in placenta

previa, may cause clots. The cryoglobulins may be responsible for retinal vascular lesions. They noted that minute vascular lesions, even if numerous, may give no clinical manifestations unless (1) the vessels lie in an area of high visibility (such as retina or skin), (2) the injured tissues are well supplied with pain receptors (joints), (3) small lesions give notable organ dysfunction (the central nervous system), or (4) injury gives useful laboratory findings (such as microscopic hematuria).

Anatomic Studies.—Wybar [59,60] made neoprene casts of the ocular circulation of 17 normal human eyes by injecting neoprene latex into the ophthalmic artery and then digesting the ocular tissues with pepsin and trypsin. He found that several branches arise from the central retinal artery within the optic nerve and may form two types of uveoretinal arterial anastomoses: (1) between the central retinal artery and the arterial plexus of the pia mater surrounding the anterior part of the optic nerve and (2) between the central retinal artery and the intrascleral circle of Zinn. He suggested that these anastomoses are important in the sequence of events of central retinal artery occlusion and also in the results of treatment. He advised using oxygen to enable the retinal ganglion cells to survive the period when the retinal circulation is at an inadequate level, before reestablishment of the circulation by collateral channels. Shea [61] found patent ipsilateral anastomoses between the ophthalmic and external carotid arteries in 91.8% of 49 perfusions of human cadavers and found patent contralateral anastomoses in 31.8% of 22 perfusions. He stated that ipsilateral anastomoses are functionally adequate to preserve vision in the event of planned occlusion of the ophthalmic artery near its point of origin. If reliance is placed on the contralateral anastomoses alone, the risk of visual loss seems considerably greater. Keeney and Barlow [62] have studied the problems of demonstrating the retinal vascular patterns in the albino rat, which are somewhat different from the problems involving human eyes. They are best demonstrated by injection of India ink into the common carotid artery in the intact animal following perfusion of saline solution or purified water.

Experimental Physiologic Studies.—Bettman and Fellows [63] studied the blood volume of the vascular structures of the intact eye by using radioactive phosphorus incubated with red blood cells, previously withdrawn from a vein and then reinjected. In this way they could test the action of various substances on the blood volume. Varying the oxygen concentration of the inspired air produced no change, but inhalation of 10% carbon dioxide caused a marked increase in the blood volume. Wudka and Leopold [64,65] described their brilliant experiments on the choroidal vessels of the eye of the rabbit in two communications which should be read in their entirety. Staenglen [66] tested the hyperemic effect of various drugs on the retinal arterioles and concluded that the phthalazines (1,4-dihydrazinophthalazine [Nepresol] and hydralazine [Apresoline]) have the most active known vasodilating effect on the retinal vessels. Wethmar [67] tested the effects of various drugs and showed that Combinstrol, a selective combination of several nitrites, produces an immediate and lasting vasodilatation. Methylenedioxybenzylmethylmethylenedioxyquinoline (Eupaverine) and tolazoline (Priscoline) given by the retrobulbar route were particularly effective vasodilators. Zahn and Simková [68] showed that intravenous levarterenol (*l*-norepinephrine) caused a significant increase in the retinal arterial pressure with a simultaneous narrowing of angioscotomas indicating increased blood supply to the retina. Mikuni [69] stated that in the presence of retinal angiosclerosis and retinal angiospasm the retinobrachial systolic pressure ratio is elevated. François and Verriest [70] found that patients with various retinal vascular affections often

had central scotomas demonstrable only under scotopic illumination. Dobree [71] measured the size of the retinal vessels in chronic simple glaucoma. He discovered that reducing the intraocular pressure from more than 60 mm. of mercury caused the vessels to narrow but, when the initial tension was less than 50 mm. of mercury, lowering the tension had no effect on the caliber of the retinal arterioles and veins. He postulated a lack of oxygen or an excess of carbon dioxide acting on the vascular walls as the cause of the vasodilatation at high levels of intraocular pressure.

Arterial Occlusions.—Abboud [72] discussed the treatment of retinal artery occlusion. He presented data on three cases, in two of which good visual improvement was obtained by retrobulbar injection, in one case with tolazoline and hyaluronidase and in the other with acetylcholine. Krasnov and associates [73] had 50 patients with hypertension and various retinal affections. The prothrombin index in 47 of the 50 was increased 112% to 280%. Thirty-eight patients also had elevated blood fibrin. Bishydroxycoumarin (Dicumarol) was given to 35 patients, aged 40 to 70 years: Sixteen of these had a central or branch vein thrombosis; eleven, an occlusion of the central artery; seven a spasm of the artery, and one, hypertensive retinopathy. Fifteen controls received no anticoagulant. The treated patients developed better visual acuity and had earlier absorption of hemorrhage. Patz [74] occluded the central retinal arteries of rats and noted that the inhalation of oxygen considerably increased the oxygen tensions of the inner portions of the retina. He found that the ganglion cell and bipolar layers had much less degeneration than did the retinas of similar animals in ordinary air. Three patients so treated one and one-quarter, four, and six hours after central or branch artery occlusion regained considerable vision under oxygen inhalation, but one patient seen four hours after onset obtained no improvement. This author also recommended cervical sympathetic block, massage of the globe, paracentesis, retrobulbar block, and vasodilators, but he did not mention anticoagulants. Heer [75] reported on a patient who had a central scotoma caused by retinal edema and presumably an infarction of the papillomacular branch of the central artery. Bellavia [76] and Klien [77] discussed Jensen's juxtapapillary retinopathy, which in Klien's opinion may in reality be a focal retinal arteriolitis.

Kearns [78] reported a case of systemic fat embolism due to trauma in which a retinopathy similar to Purtscher's traumatic retinal angiopathy appeared. The diagnosis of fat embolism was made clinically, and, at necropsy, intravascular fat particles were demonstrated in the flat retinal preparation. This suggests that Purtscher's traumatic retinal angiopathy and fat embolism of the retina may be the same entity. Pünder and Schmidt [79] reported on two cases of post-traumatic fat embolism of the retina, both with good recovery and with no permanent ocular damage. Schenk [80] described two cases in which cotton-wool patches appeared in the retina several days after the common carotid artery was ligated as treatment for unilateral traumatic carotid-cavernous sinus fistula with proptosis of the eye on the involved side. This author found three similar cases in the literature. He postulated that the phenomenon was caused by passive venous congestion and resultant serous extravasation. I am preparing a paper on similar retinopathy which appeared after common carotid or internal carotid ligation and also after spontaneous thrombosis of the internal carotid artery, in which the retinopathy almost certainly resulted from hypotension induced in the ophthalmic artery. Retinal artery pressures measured with the ophthalmodynamometer all showed a reduction of the diastolic level to near zero in the affected eye, with normal or elevated pressure on the side of the patent carotid artery.

Temporal Arteritis.—Venturi [81] reported a single case. Bennett [82] discussed six patients who had sustained visual loss. In his

opinion, some recovery of vision occurred under treatment with cortisone, using 150 mg. daily for one week, 100 mg. daily for one week, 50 mg. daily for one week, and finally 25 mg. daily for a variable period. He treated all patients with vasodilators, one with anticoagulants, and one with chlortetracycline (Aureomycin). Four of the six seem to have recovered a little vision, and none regressed.

It is my opinion that the prevention of further visual loss is the most important consideration in therapy. Recovery of vision once the vision is lost is rarely of significant degree. Early diagnosis and therapy, therefore, before visual loss has occurred, are imperative. I believe that the initial therapy should be started with at least 300 mg. of cortisone daily for 10 days to 2 weeks, followed by gradual reduction to 100 mg. daily during the next month, and then gradual reduction to a lower maintenance dose for a variable period. Vasodilators should not be used, but carbon dioxide and oxygen are valuable, and anticoagulants are indicated in the presence of recent visual loss.

Venous Occlusions.—Klien and Olwin [83] surveyed the pathogenesis of retinal venous occlusions and then discussed the use of anticoagulants on 53 patients. They concluded that this treatment should be started immediately when a patient presents himself with a retinal venous occlusion or with an imminent occlusion. In Barsky's [84] opinion, both anticoagulants and steroid therapy should be used. Morgan [85] advocated anticoagulant therapy and mentioned a patient who was treated for a year with heparin, without success, but whose vision improved immediately after leeches were applied. He urged that research on hirudin might be worth while. Montagne [86] used 3-(1-phenylpropyl)-4-hydroxycoumarin (Marcoumar, Roche), which has a prolonged action. Mikuni and Ibaraki [87] treated successfully five patients with insulin-free pancreatic extract (Padutin), a hypotensive drug, and observed a marked retinal vasodilatation. Cuendet and associates [88] reported the case of a 43-year-old man with recurrent thrombosis of the central veins associated with multiple infections, polycythemia, thrombophlebitis of the legs, and hypersensitivity to penicillin and to old tuberculin but who had no improvement under treatment with aminosalicylic acid (PAS) and streptomycin. Smith [89,90] discussed 14 patients and four pathologic specimens with both glaucoma and central retinal vein occlusion. He noted that glaucoma follows the occlusion and rubeosis iridis in the usual type of thrombotic glaucoma. He observed that occasionally the glaucoma occurs first and produces the central vein occlusion, and then later there may be a superimposed thrombotic glaucoma with rubeosis.

Electroretinography.—Karpe and Uchermann [91] stated that the characteristic electroretinogram of embolism of the central retinal artery is that designated negative-minus (where the a-wave is increased but the b-wave is decreased). This type of wave pattern indicates a poor prognosis. The electroretinogram is inappreciably affected by a branch embolism. A normal, subnormal, or negative-minus electroretinogram is usual in the presence of a thrombosis of the central retinal vein or branch vein. The prognosis for vision is fairly good with a normal or supernormal electroretinogram but poor if the electroretinogram is negative-minus or subnormal. Henkes [92] reported a supernormal electroretinogram in patients who had hypertension without arteriosclerosis and a subnormal electroretinogram in patients who had arteriosclerosis without hypertension. He interpreted this supernormal response as indicating a raised irritability of the retinal neurons resulting from hampered oxygen supply following retinal vasoconstriction. The subnormal response is ascribed to a totally insufficient oxygen supply.

Chorioretinitis in Toxoplasmosis

The problem of making a definitive diagnosis in each case of chorioretinitis continues to be a disturbing one and has not been advanced appreciably during the past year. The participants in a conference on granulomatous uveitis, reported by Hogan,[93] concluded that the interpretation of dye-test results as related to ocular toxoplasmosis was difficult and inconclusive. They thought that a negative dye test in a child less than 10 years of age would probably rule out toxoplasmosis. They considered the skin test of little value except as a screening device, and the complement fixation test was considered to be of no practical value. Therapy of suspected toxoplasmic uveitis with sulfadiazine alone and combined with pyrimethamine (Daraprim) showed varying results. Sabin[94] presented a very extensive review of toxoplasmosis with particular reference to the eye. Burnham and Beuerman[95] treated eight patients who had presumed toxoplasmic uveitis with sulfadiazine and pyrimethamine. Four improved rapidly, and four, slowly. Swan and French[96] reported on a case of congenital toxoplasmosis in an infant who had no convulsions but who had a high dye test titer and unilateral central chorioretinitis. The mother also had a high titer. François and associates[97] enucleated an eye because of a progressively enlarging mass near the optic disk of a 3-year-old child. This proved to be a granulomatous lesion, which caused the authors to postulate toxoplasmosis, although no organisms were demonstrated.

Straub[98] summarized his experiments in producing toxoplasmic eye lesions in rabbits and guinea pigs and later wrote an excellent monograph[99] on the subject. Arribas and Schlaegel,[100] Jacobs and associates,[101] and Hogan and associates[102] produced toxoplasmic lesions in the eyes of rabbits, causing very high dye test titers. The latter group of authors recovered viable toxoplasmas from such tissues up to 10 months after inoculation. O'Connor[103] described the agar-diffusion technique as a method of detecting antitoxoplasma precipitins in the aqueous humor. Frenkel[104] discussed the incidence of positive toxoplasma tests among patients with uveitis. He found the number greater than among the general population.

The Retina in Various Systemic Diseases

The retina is involved in so many systemic diseases that the tremendous literature can only be mentioned briefly here. Bennett[105] reported a comprehensive study of 332 patients who had uveitis. He devised a classification based on three positive associations and has accordingly divided his cases into four groups: Group A includes uveitis associated with systemic disease of the collagenous or rheumatic type; Group B includes uveitis of purely local (ocular) origin, perhaps due to virus infection; Group C includes those who have systemic and ocular granulomatous disease, and Group D is made up of the unclassified cases. Among his patients there was not a single case proved to be due to tuberculosis, to brucellosis, or to infectious mononucleosis. He urged that expensive clinical investigation be replaced by accurate history-taking and clinical study, for much of the routine of general examination in such cases is worthless. This concept is confirmed by Edling,[106] who studied the frequency of roentgenologic signs of sinusitis in patients with uveitis. He found sinusitis unimportant as a cause. Kimura[107] reported that about 5% of patients in tuberculosis sanatoria give a history of phlyctenule and 2.7% give a history of other ocular tuberculosis. In his opinion, the testing of the lactic acid coagulation has greater value than the blood sedimentation rate in the diagnosis of ocular tuberculosis. Dufour[108] wrote an excellent monograph and showed 21 well-documented cases of proved or probable systemic tuberculosis which had associated ocular lesions of tuberculosis.

Kraffel [109] described a peculiar form of bilateral chorioretinitis of undetermined etiology in which tongue-like areas of this lesion extended out from the optic disks.

Boase [110] recorded the first two reported cases of Coenurus cysts affecting the ocular structures. One was orbital and the other intraocular. These cysts develop from the ova of Multiceps multiceps, a common parasite of dogs, who get the disease by eating the brains of sheep afflicted with "blind staggers." Couran and Waddy [111] stated that many patients with ocular lesions of onchocerciasis had made a good recovery under treatment for five weeks with suramin sodium (Antrypol) in weekly doses of 1 gm., given intravenously.

Somerset and Sen [112] searched specifically for leprous lesions of the fundus among 224 lepers. They found two patients with small discrete nodules or pearls about 0.25 mm. in diameter situated on the retina, exactly similar in appearance to the well-known iris pearls. Each patient had had the disease for at least 25 years. The lesions in one patient healed, while those in the other remained unchanged for six months.

Torrents and associates [113] made electroretinograms on three hyperthyroid patients before and after treatment. The b-wave potential was elevated from the normal 0.40 mv. to a level between 0.48 and 0.70 mv. Treatment resulted in more normal levels. In myxedema the b-wave potential was lowered. In both states the duration and latent period of the b-wave were increased.

Ocular Sarcoidosis.—Crick [114] found 33% ocular involvement among 63 cases of sarcoidosis with positive biopsies. Anterior uveitis was the commonest lesion, occurring among 17 of the 21 cases, but only 5 of these were nodular. Thirteen had chorioretinal lesions, characterized by multiple discrete rounded foci of inflammation: Some had chorioretinitis, and some had only retinitis. Often a characteristic round and woolly vitreous opacity appeared to settle on the retina in the lower part of the fundus. Systemic administration of cortisone seemed to be the treatment of choice; streptomycin, aminosalicylic acid, and isoniazid gave disappointing results. In the discussion, D. G. James [115] stated that the Kveim test was positive in 72% of cases. Ainslie and James [116] noted that no eye signs are sufficiently characteristic to enable one to diagnose sarcoidosis and that other clinical or radiologic confirmation is necessary. The best diagnostic support comes from biopsy of skin lesions or enlarged lymph nodes. Eye signs were present in 28 of 100 cases. Morax [117] discussed unusual ocular lesions of sarcoidosis and presented a patient who had a tumor of the optic disk, choroiditis, and perivenous nodules, together with systemic manifestations. Another patient had a sarcoid nodule compressing the optic nerve. Cross [118] reported on three patients with perivasculitis retinae among 23 patients who had ocular sarcoidosis; all three improved under treatment with subconjunctival or intratenon cortisone.

Collagen Diseases.—Constantine [119] introduced a symposium on the so-called diffuse collagen diseases, discussing the systemic manifestations of periarteritis nodosa, dermatomyositis, scleroderma, and disseminated lupus erythematosus. Zimmerman [120] then reviewed the anatomy, physiology, and pathology of the connective tissue. Maumenee [121] discussed the ocular manifestations and called attention to the frequency of cotton-wool patches and hemorrhages in the retina, of papilledema, and of transudates and leukocytes in the choroid among patients with these diseases. Also he noted that such changes were absent in rheumatoid arthritis and rheumatic fever, an observation previously recorded by Hollenhorst and Henderson.[122] Maumenee further noted the occurrence of episcleritis and scleritis with periarteritis nodosa, rheumatoid arthritis, and dermatomyositis, and in the first two with scleromalacia perforans, necrotizing scleritis and keratitis, and marginal corneal ulcers. Guyton [123] reviewed the differential diag-

nosis, and Contardo,[124] the importance of the ocular manifestations of these diseases. Leopold [125] terminated the symposium with a discussion of the therapy. The most important therapeutic agents are the steroid compounds, used locally, systemically, or both. He also considered the use of salicylates, gold, phenylbutazone, transfusion, anticoagulants, and roentgen therapy.

Boeck [126] called attention to the markedly diverse ocular manifestations of periarteritis nodosa in the eye. These stem from three major sources: (1) local involvement of the ocular and orbital arterioles, (2) similar lesions elsewhere in the body (kidneys and central nervous system), and (3) changes of undetermined origin. Garcin, Man, and Gruner [127] showed beautiful colored photographs of the histologic changes in the choroidal vessels of a patient who had died of this disease and had papilledema and exudative retinal detachment in each eye, but normal blood vessels. Kittel's [128] patient had bilateral central artery occlusion in a presumed case of polyarteritis nodosa.

Cury, Breakey, and Payne [129] described an interesting patient who had what the authors called "allergic granulomatous angiitis" involving the right eye and orbit. Clinically, this eye had uveoscleritis. The other eye had papilledema, which later subsided. This elderly patient had anorexia, loss of weight, severe weakness, and enlarged liver, eosinophilia, and an elevated sedimentation rate. Histologically, the eye showed the changes which prompted the designation of the disease.

Müller [130] reported two cases of hypopyon uveitis characterized by obliterating angiitis and periangiitis. Patchy chorioretinal lesions corresponded to the system of terminal vessels in the choroid. Papillitis and retinal hemorrhages were also present.

Zetterström and Berglund [131] observed 11 children aged 13 years or less who developed systemic lupus erythematosus. Of the 11, three had papilledema, exudates, and hemorrhages into the retina.

Unusual Vascular Diseases.—Appelmans and associates [132] reported a case of the pulseless (Takayashu's) syndrome with the characteristic triad of (1) absent radial pulse, (2) retinal vascular changes, and (3) cataract. The disease is a progressive thrombosis of the carotid and subclavian arteries, hypercoagulability of the blood platelets, and, sometimes, an elevation of the blood platelets. Pinkham [133] reviewed the 68 Japanese and 38 non-Japanese cases reported. The ocular findings are extremely interesting and include reduced retinal artery pressures, fragmentation of the retinal blood column, peripheral arteriovenous anastomoses, optic atrophy, large irregular veins, retinal hemorrhages, aneurysms of the terminal arterioles, cataracts, mydriasis, iris atrophy, neovascularization of the iris and retina, and sludging of the conjunctival blood stream. The cases of this syndrome for the most part fall into two main groups: (1) those of syphilitic origin, with syphilitic aortitis, and (2) those caused by a nonspecific arteritis confined to young females, 15 to 38 years of age. The case reported by Trias De Bes and associates [134] had typical findings.

Kimura, Carriker, and Hogan [135] presented an important paper dealing with the ever-disturbing problem of retinal vasculitis and recurrent hemorrhage into the vitreous. They studied 21 cases clinically and examined another 19 eyes histologically, but they were unable to determine the etiology. They could not demonstrate either tuberculosis or other specific disease entities in the pathologic specimens. This study serves to reemphasize the inadequacy of our present diagnostic tests for this disease. The authors advocated treatment of selected cases of their "primary" type with antituberculous therapy and treatment of the type secondary to iridocyclitis with steroid therapy, sometimes combined with antituberculous medications. François and De Rouck [136] found that there is a normal electroretinogram in the early stages of periphlebitis retinae so long as there is no retinitis proliferans or detachment of the

retina. If the retina degenerates, the electroretinogram becomes subnormal, and all the more so as the degree of degeneration becomes worse. Franceschetti and Forni [137] treated 11 cases of Eales' disease by surface diathermy. Five eyes had not had a vitreous hemorrhage and eight had. All patients that were followed postoperatively had successful results except one, in whom iridocyclitis developed eight months later.

Blood Dyscrasias.—Kearns [138] discussed the changes in the retina of anemia, polycythemia, leukemia, purpura, sickle-cell anemia, disseminated lupus erythematosus, and infectious mononucleosis. Wasilewski [139] examined 33 patients given 297 transfusions. All had abnormalities of the blood. In 12 of them ocular hemorrhages developed: They were preretinal in 11; retinal in 1, and 2 were mixed. Some patients had more than one hemorrhage. Brihaye-van Geertruyden [140] saw cotton-wool patches in the retina of a patient with Hodgkin's disease; on histologic examination these proved to be cytoid bodies and not lymphomatous tissue. Cucco and Pende [141] examined 10 cases of multiple myeloma and found a high incidence of fundus changes consisting of retinal hemorrhages and choroidal lesions. They postulated that thrombocytopenia, disturbed coagulation time, and toxic endothelial changes caused the lesions. Bronstein [142] presented pathologic sections showing infiltration of the iris, choroid, and sclera with cells of multiple myeloma. This seems to be the first such case reported. Apparently no ocular examination was done during life, and so the clinical manifestations are unknown. All other reports of ocular involvement have described retinal hemorrhage, toxic retinopathy, central vein and artery occlusions, papilledema, ocular nerve palsies, one case of intraocular plasma-cell tumor, orbital myeloma, and visual field defects. Danis, Brauman, and Coppez [143] described two cases of multiple myeloma with cryoglobulinemia with dilatation and tortuosity of the retinal veins, diffuse hemorrhages and some cotton-wool patches, sludging of the arterial and venous blood on compression of the globe, and reduction of visual acuity. They ascribed these changes to the hyperproteinemia. Myerson and Stout [144] and Ellis and Klotz [145] discussed cryoglobulinemia and the ocular manifestations, which are essentially as already described. These authors reported one case with occlusion of a central artery, scleroderma, and gangrene of the digits.

Degeneration of Elastic Tissue.—Keith [146] reported on a patient who had angioid streaks associated with pseudoxanthoma elasticum, and he reviewed the literature on the subject. He stated that 59% to 87% of patients with angioid streaks have associated pseudoxanthoma elasticum and 9% have osteitis deformans (Paget's disease). Eight per cent of patients with the latter disease have angioid streaks. Liegl [147] reported on a 12-year-old patient who had pseudoxanthoma elasticum and multiple pigmented drusen in each eye, but no angioid streaks. Valenzuela Encina's [148] case had no systemic disorder associated with the angioid streaks. Bischler [149] described a fundus picture consisting of many fine whitish-yellow or greyish-brown dots which either cover the fundus evenly or are restricted to circumscribed areas. These are caused by thickening of the cuticular layer of Bruch's membrane with localized loss or accumulation of pigment. Similar lesions are seen and described in association with angioid streaks and with or without systemic elastorrhexy. She described three cases.

Diseases of the Nervous System.—Renard and Brégeat [150] reviewed seven cases with atypical vascular anomalies of the retina and noted an association with vascular anomalies of the brain, viscera, and skin. Dollfus,[151] in discussing this paper, also presented seven similar cases. Doden and Adams [152] examined 947 patients with periphlebitis retinae. The morbidity from multiple sclerosis was 0.5%, in comparison with the morbidity of the mean population (0.4%). Twenty per cent of 80 patients who had multiple sclerosis had sheathing of

the veins, but no extensive hemorrhage or proliferation, and thus differed from patients with periphlebitis retinae. None had either intracranial hemorrhage or thromboangiitis obliterans, but 96 of the 947 had a variety of neurologic findings. Orbán [153] observed perivenous sheathing among 21 of 50 patients who had multiple sclerosis. Schwab [154] listed seven patients with tuberous sclerosis, of whom five had retinal tumors. One patient had both a tumor of the disk and three chorioretinal scars.

Leipert [155] described a most interesting 34-year-old woman who reported for therapy of cachexia and other signs of Sheehan's syndrome. At admission the eyes were normal, but the following day she had lipemia retinalis. Total blood fats were 4.4%. In the right eye, at the same time, there appeared a markedly cloudy aqueous, which was found to contain 10% fat. Healing occurred under treatment with thyroid hormone and a fat-free diet. The diagnosis was hyperlipemia due to secondary hypothyroidism in the course of Sheehan's syndrome.

Reynon and Masbernard [156] observed severe hypertensive angiospastic retinopathy in a patient who had acute intermittent porphyria. The fundi returned to normal when the general signs of the disease receded. The authors suggested that the neurologic and clinical manifestations could be on a vasospastic basis.

Remky [157] measured the retinal artery pressure with the ophthalmodynamometer and noted an increase of pressure when the patient changed from the sitting to the supine position. This was more marked in the young than in the old, was minimized by epinephrine, and was almost absent in hypertensive patients. Lifting a weight caused an increase in the pressure, while rotating the head caused a unilateral rise. Bailliart [158] and Paufique and Moreau [159] discussed the syndrome of isolated cerebral orthostatic hypotension manifested by vague headaches, dizziness, or fainting spells and diagnosed by noting the fall of the retinal artery pressure to hypotensive levels on assuming the sitting or standing positions. The latter administered distilled water intravenously as the therapy of choice.

Puig Solanes [160] summarized and discussed 14 cases of Vogt-Koyanagi disease and reviewed their clinical aspects.

Retinal Detachment

McLean and associates [161] in a symposium discussed the problems of diagnosis and surgical treatment of retinal detachment, with emphasis on some of the practical points in the therapy of this condition. Thiel [162] made measurements of the situation and form of the ora serrata and described the physiologic and pathologic peripheral cystoid spaces. Samuels [163] showed that these spaces are actually connected together like a string of pearls. Fison [164] and Brockhurst [165] discussed in detail the techniques and advantages of using indirect binocular ophthalmoscopy. Verhoeff [166] commented on the clinical portent of "Moore's lightning streaks" and expressed the opinion that the typical phenomena described by Moore come from shrinkage of the vitreous. If no retinal separation is found at examination, there is little danger of its developing later. Mundt and Hughes [167] investigated the ultrasonic "reflectoscope" and decided that it might have value in differentiating simple serous detachments from those due to tumors or hemorrhage, but they made no claims for it. Graupner [168] reported cases of vitreous hemorrhage in which he found retinal tears causing the bleeding. In all cases there was marked cystoid degeneration. Marchessi [169] noted a similar case.

The subretinal fluid was analyzed by Alajmo,[170] who found histamine in three of four cases; by De Vincentiis,[171] who confirmed the presence of cholinesterase, and by Dorello,[172] who did electrophoretic studies. Dorello found that the higher the protein content the more the electrophoretic pattern resembled that of the plasma. He concluded that the protein in the subretinal fluid is derived from the blood.

Etiology of Detachment.—Adams [173] described retinal breaks in three eye-bank eyes. The round holes had a single strand of vitreous attached to the operculum, but the edge of the hole itself was free from vitreous attachment and retraction. The extreme end of the flap of the horseshoe tear was pulled back by a vitreous adhesion. The inner limiting membrane halfway to the ora serrata was tented up by multiple adhesions. The posterior edge of the horseshoe tear showed no evidence of vitreous attachment. Hagedoorn and Sieger [174] presented most interesting photographs of congenital retinovitreal adhesions which, they postulate, may be concerned in the formation of flaps and opercula in cases of idiopathic as well as other forms of retinal detachment. Michaelson [175] discussed a series of cases showing foci in which retinal holes were preceded by a pigmented choroidopathy and then by local retinal phlebosclerosis.

Prewitt [176] reported a case in which idiopathic retinal detachment occurred in a patient with peptic ulcer, gastritis, pylorospasm, a heart attack, and other disturbances. He suggested that the detachment was due to mental stress in a person with a high somatic sensitivity. Lincoff, Wise, and Romaine [177] described three interesting retinal detachments, all of which occurred following the iridocyclitis accompanying herpes zoster ophthalmicus. In one patient a hole was found and treated. There was a tendency to spontaneous reattachment in all three cases. In the authors' opinion, the detachments arose from exudative choroiditis.

Ourgaud and Bérard [178] noted that, when the retina was detached and the eye was hypotonic, fluorescein disappeared more slowly from the anterior chamber than when the eye was normal. After operation, such an eye usually had a return to normal tension and to normal fluorescein elimination. The authors discussed the impairment of production of aqueous, reduction in the coefficient of resistance to outflow of aqueous, and increased permeability of the blood-aqueous barrier, all of which are noted with retinal detachment. They described the difficulties of management of patients with both glaucoma and retinal detachment. Nesserov [179] reported successful diathermy in a case of this type; the postoperative period was complicated by an attack of acute glaucoma.

Jaeger [180] reported on an interesting family tree in which one parent and three of his seven children had bilateral obliteration of the peripheral branches of the inferior temporal vessels. In one patient this led to a disinsertion of the retina and retinal detachment at the ora serrata. Frey [181] successfully did diathermy on the bilateral retinal detachments with symmetrical disinsertion which occurred in two 13-year-old boys.

Pau [182] examined histologically two eyes with recent detachment. The degenerated areas in the retina proved to be thinned retina in which true retinal elements were replaced by vascular connective tissue and pigment epithelium. Vitreous strands were attached to the peripheral and posterior margin of the sclerotic area, and the tear occurred at its posterior margin.

In Abboud's [183] opinion, the retinal detachment caused by the instillation of isoflurophate (DFP) is due to severe congestion of the uveal tract leading to transudation of fluid between the choroid and retina. The ciliary muscle then pulls on the retina and perhaps ruptures a cyst in the peripheral retina. In Weekers and Lavergne's [184] opinion, the traction exerted by the ciliary muscle is the major cause.

Experimental Surgery.—Asbury and Vaughan [185] described experimental scleral surgical procedures on 14 monkey eyes, including lamellar scleral resection (with and without diathermy), full-thickness scleral resection (single and multiple), and the scleral buckling operation of Schepens (with and without diathermy). The eyes were later enucleated and examined histologically. No retinal detachments were produced before or after operation. The authors considered the monkey a very satis-

factory animal for experimental scleral surgery. In both types of scleral resection, the inflammatory reaction was sufficient to cause chorioretinal adhesion. No conclusions were reached procedurally.

Everett [186] carried out a comparative study in healthy rabbit eyes of the four basic shortening operations in use today: penetrating scleral resection, lamellar-scleral resection, lamellar-scleral resection with polyethylene tubing, and the scleral fold. He favored the scleral fold. In a later paper [187] he described two modifications of the original technique; he abandoned the separation of choroid and sclera, and he excised the top of the scleral fold. Dellaporta [188] performed a scleral buckling operation and incorporated polyethylene tubing in the eyes of dogs, producing a permanent cylindrical protrusion of the sclerochoroid and retina into the interior of the eye. He advocated a scleral resection in the area into which the tube was to be inserted. This would prevent unfolding of the scleral fold.

Capper and Leopold [189] showed experimentally that both hypotonia and trauma to the sclera were necessary to produce serous detachment of the choroid. Linnen and Hammers [190] found that choroidal detachment more frequently followed repeated trauma than single traumatic incidents. Dyster-Aas and Krakau [191] carried out diathermy of the retina with a transbulbar minute electrode. They suggested the applicability of the method to therapy of Eales' disease and to cauterization of choroidal melanomas and to remove nonmagnetic intraocular foreign bodies. No human eyes were used. Knoll [192] measured experimentally the amount of heat and scleral shrinkage, and their effect on the intraocular pressure, produced by electrosurgical treatment.

Prognosis.—Shipman and Luce [193] reported on 606 patients with retinal detachments and found that 12.4% of the detachments were bilateral. This approximates the averages of 15 other authors whom they cited. They stressed the importance of making every effort to preserve the vision of the eye with the initial detachment. Odic and Nectoux [194] found that among 310 patients with retinal detachment, of whom there were records in the files of the Parisian Social Security office, 243 had less than 0.1 vision. Such preponderance of poor vision was ascribed to the severity of the cases registered and to the low standard of living of the subjects.

Funder [195] investigated the fate of 92 patients who lost all vision in one eye from idiopathic retinal detachment. The average follow-up was four years and seven months. Only 28 of the 92 patients retained a healthy remaining eye. Nearly one-third of all the patients (29 patients) became completely blind, and, of these, 19 were blind from bilateral detachment. Ten had uncomplicated aphakia, nineteen had extremely high myopia, twenty-six had idiopathic retinal detachment, and nine had some other disease. Funder [196] reported 89 cases of aphakic retinal detachments. In his three papers he noted that the incidence is increasing because of longevity and is greater among men than among women and that many detachments are delayed several years in their onset. Discission of juvenile cataract favors retinal detachment. Funder prefers diathermy combined with eyeball-shortening as the best procedure.

Results of Surgical Treatment.—Taubitz [197] used only Weve's diathermy coagulation and obtained 53.5% reattachments among 206 detachments. Thirteen of forty-four total detachments and ten of nineteen aphakic detachments were cured. Klomp [198] used only diathermy and cured 60.1% of 713 patients. Repeated operations were necessary in 89 patients. Only 26 cures were obtained among 76 patients with no detectable retinal holes. Ten patients were treated with a complete circular barrage; five of these were cured. Vom Hofe [199] noted 106 recurrences among 573 operations. In 27 the tear was extensive and had not entirely closed; 12 of these were cured. In 55 new tears appeared; 12 were cured.

Of 18 eyes on which operation was performed three times, only 4 were cured.

Asbury and Vaughan [200] found that 64% of 103 patients on whom operation was performed in a teaching hospital were cured, in contrast to 75% of cures among 376 patients on whom private ophthalmologists operated. If the latter surgeons did not include patients who had previously undergone operation elsewhere, the cure rate was 81%.

Vit [201] obtained successful reattachment in half of 21 cases of unfavorable retinal detachment, using lamellar scleral resection combined with diathermy closure of the retinal hole. Shapland [202] asserted that the operation of lamellar scleral resection improves the over-all prognosis of operations for detachment by some 15%. Hruby [203] reported 62% cures among 50 unfavorable cases in which the method of combined diathermy and penetrating scleral resection was used. Nataf and associates [204] and Schiff-Wertheimer and associates [205] advocate scleral resection only for difficult cases or as a last resort.

Colyear and Pischel [206] presented an interesting group of 26 cases in which retinal tears were found but no retinal detachment had occurred. In 40% of these a detachment did not develop within the period of observation; in 20% detachment did develop, and in 40% prophylactic operation was successful. The authors recommended the latter course as the procedure of choice. The majority of the group in which the retina did not detach had a freely floating operculum in the vitreous or had an old chorioretinitis, and all had only a single tear. All those whose retina did detach had tears above the horizontal, and all but one had vitreous adherent to a flap of retina which remained attached to the margin of the tear.

Surgical Techniques.—Arruga [207] stated that it is always difficult to know when to operate and what type of operation to use. He does surface coagulation in recent detachments with a small tear, but in recent detachments with multiple tears he waits and lets the retina settle maximally and then does surface diathermy. If the retina does not settle, he treats the patient with antibiotics and corticosteroids for 15 days and then does surface coagulation. If this fails, he waits for three weeks and does scleral resection and diathermy. In all detachments with extensive tears he does scleral resection above and behind the tear. He uses air in the vitreous routinely.[208] He uses light diathermy over the macular area when there is a hole in the macula. Marin-Amat [209] recommended extensive and intensive diathermy coagulation in otherwise inoperable cases to impair the secretory function of the choroid and to cause scleral shrinkage.

Jayle [210] described a modification of the lamellar sclerectomy by making a thick wing-shaped scleral flap and then accomplishing the scleral shortening by mattress sutures inserted at the hinge of the flap and pulled through the limbal lip of the incision. Of 20 cases in which operation was performed, there were 13 reattachments, 4 partial reattachments, and 3 failures. Chamlin and Rubner [211] presented an ingenious method of producing scleral buckling by incising nearly through the sclera in outlining a strip one-third to one-half the circumference of the globe and 5 mm. in width. They then undermined this strip on both sides, after which the strip contracted to a width of 1.5 mm. After aspiration of subretinal fluid and such diathermy as was necessary, the two edges of intact sclera were approximated so as to bury the isolated strip and thus buckle the sclera.

Meyer-Schwickerath [212] continues his investigations on treatment of retinal detachment by light-coagulation. He first reported this in 1954 [213] and most recently [214] presented statistics on its use for various types of retinal disease commonly treated by electrodiathermy. He reported successful iridotomy with it.

Complications and Side-Effects of Surgery.—Colyear and Pischel [215] surveyed 440 patients with retinal detachments and cured 75.5%. Of those on whom operation

had been performed unsuccessfully elsewhere previously, 45.1% were cured. Patients on whom the primary operation was done by the authors had a cure rate of 81.1%. Poor results emanated from failure to close the original tear, failure to locate the original tear or tears, and the later development of other tears after apparently successful operation. Swan, Christensen, and Weisel [216] examined for evidence of choroidal detachment 32 patients on whom operation for retinal detachment had been performed. Fifteen of eighteen treated by scleral imbrication and diathermy, three of nine treated by diathermy and removal of subretinal fluid, and none of five treated by surface diathermy had a choroidal detachment. All in whom this developed were hypotonic, and in every such case there was a flattened sclera induced either by heat shrinkage or by imbrication. Dellaporta [217] described severe hypotonia which developed after successful intracapsular operation for cataract and later cyclodialysis or choroidal detachment. This was followed by papilledema a month later and by circumscribed macular edema and fine subretinal pigment lines in the nasal fundus of three of the four eyes. Follow-up showed that the hypotonia caused the macular changes but that degenerated vitreous and advanced age probably played a precipitating role. Maggi Zavalia and Zurbriggen [218] found a definite hypesthesia or anesthesia of the cornea over its whole surface or in the quadrant corresponding to previous scleral resection. This was present in each of eight patients and persisted in some as long as a year and in one patient gave rise to a severe corneal ulcer.

Badtke [219] reported on 11 patients whose one eye was enucleated for a suspected intraocular malignant lesion. In these, a uveal hemangioma was found in five, a massive subretinal hemorrhage in one, subretinal connective tissue in three, tuberculoma in one, and a retinal detachment with melanosis in one. A 12th, whose eye was not enucleated, proved to have an intraocular foreign body with a connective tissue reaction around it. Bettman and Fellows [220] discussed the differential diagnosis of dark lesions of the posterior fundus. Dahlberg-Parrow [221] presented data on three cases of bilateral pseudoglioma which appear due to a primary retinal dysplasia, inherited by recessive and sex-linked transmission. These patients all had grave mental deficiency. Reese and Jones [222] described and illustrated seven cases that they considered to be cases of benign melanoma of the retinal pigment epithelium. One pathologic specimen was obtained. This showed excessive retinal pigment epithelium, and in the choroid beneath the site of the reduplicated epithelium the melanoblasts were also more pigmented. The authors considered them to be congenital lesions. Halldén [223] reported on a malignant melanoma of the choroid in which the initial sign was a retinal detachment with severe scleritis and fibrinous exudate on the detached portion of the retina. Diagnosis was made by subretinal paracentesis after the scleritis had subsided.

Eoche-Duval, Hervouet, and Lenoir [224] described a meningioma involving the posterior pole of a microphthalmic eye. This tumor enlarged and detached the retina. Histologic examination showed an intrachoroidal mixed-cell meningioma with psammoma bodies, continuous with a similar tumor of the optic nerve sheath. The authors postulated a possible intraocular origin. Nover [225] reported on a small number of patients who had several types of primary malignant lesions occurring in the eye and other parts of the body simultaneously. McLean [226] reported on three patients who had retinal tumors of glial nature, probably a manifestation of tuberous sclerosis; however, the tumors did not have a typical mulberry appearance. All these eyes were examined histologically, and the retinal tumors were glial tissue.

Vogel and Naib [227] described the characteristics of growth of a rabbit neoplasm (Vx2 carcinoma) transplanted into the rabbit fundus. They recommended this neoplasm as an experimental tool to evaluate

methods of treating intraocular neoplasms. Their material was transplanted into the subretinal tissues. They found it necessary to irradiate a wide area about the tumor to accomplish complete destruction. Cautery was effective only if the body of the tumor and a wide border about it were thoroughly coagulated. Chemotherapy (mechlorethamine [HN_2] or triethylene melamine [TEM]) was more effective combined with cautery than was either chemotherapy or cautery used alone.

Terner, Leopold, and Eisenberg[228] reported on 262 cases of ocular lesions in which radioactive phosphorus (P^{32}) uptake studies were done. Tests were made 1 hour and 24 hours after injection of the radioisotope. The test was considered positive when there was more than 30% greater than normal uptake in 1 hour and an increase beyond the 1-hour calculation in 24 hours. There were intraocular lesions in 233 cases; the remainder were adnexal. Three false-positive tests were obtained among the group of inflammatory lesions, three false-negative tests among 30 cases of intraocular malignant melanoma, and five false-negatives among 6 cases of retinoblastoma. One false-negative test occurred among the 29 adnexal lesions, in a case of basal-cell epithelioma of the eyelid. The authors consider the method to be of definite value. Owens, King, and Wells[229] and Palin and Tudway[230] concur, and they likewise believe the 24-hour count to be most significant.

Retinoblastoma.—Herm and Heath[231] reviewed 176 patients with retinoblastoma observed during the period 1897 to 1951. Of these, 79 could be adequately followed. In 25% of the 79 the lesions were bilateral. The mortality rate in the bilateral cases was 21%, and in the unilateral cases it was 23.2%. The survival rate before 1930 was 66.7%, and since then, 79.5%. Bilateral lesions were more frequent among the children of survivors. Tumors with rosettes invaded the optic nerve as frequently as those which had no rosettes. The latter more frequently entered the choroid or had extrascleral extension. No such patients survived. Reese and associates[232] treated 35 patients with bilateral lesions by enucleating the more involved eye and treating the other with triethylene melamine and irradiation. Of the 35, there were 19 who had satisfactory improvement. Eight lesions responded well for a time and then after 6 to 18 months began to grow again. The combined therapy seems better than the irradiation alone. Nonnenmacher[233] saw 22 unilateral and 8 bilateral cases. He treated them with enucleation and irradiation.

Nover and Oehlert[234] described metastases from a unilateral retinoblastoma to the brain, bones, lymph nodes, liver, and both ovaries. They suggested that the postmortem findings of multiple cartilaginous exostoses indicated that the child had a tendency to tumor formation. Valière-Vialeix and associates[235] reported on a tumor of the retina which appeared in a 45-year-old man. It was a sharply outlined white round and slightly raised tumor between the disk and macula. Since it grew rapidly, the eye was enucleated. The tumor originated in the inner layers of the retina, infiltrated all the layers, entered the choroid, and encroached on the optic nerve. The tumor cells consisted of astrocytes and microglia. Inside the tumor were calcospherites. Steward, Smith, and Arnold[236] collected 15 case reports of spontaneous regression of retinoblastoma from the literature and added one of their own. Two boys had bilateral retinoblastoma. Their father was 37 years of age, and since childhood one eye had been blind and shrunken. Diagnosis of retinoblastoma had been made when he was 3 years old, but no treatment had been given. The eye histologically showed calcified tumor cells. The intact eye had remnants of a lesion seen ophthalmoscopically; this was presumably healed retinoblastoma.

Joyce and Scott[237] suture radon seeds to the sclera over the site of melanomas and retinoblastomas. Sébas[238] recommends the routine aspiration of eyes with suspected

retinoblastoma to prevent unnecessary enucleation in cases of pseudoglioma. Davies and Thumim [239] reported on a 34-year-old man with a suspected intraocular melanoma which proved to be a cavernous hemangioma of the optic disk and retina.

Angiomatosis Retinae.—Handl [240] described three young patients whose von Hippel lesions were improved with electrocoagulation. Scleral resection was performed on one patient to replace a detachment, and the angioma then became visible. Handl advocates early electrocoagulation in preference to radium, roentgen irradiation, or electrolysis to best preserve vision. In his opinion this treatment is best even when secondary changes exist in the retina. Kronenberg [241] and Charamis [242] agree with this. The latter stresses the importance of using a high-intensity current of 50 to 70 ma. for surface coagulation and a current of 40 to 50 ma. for the 2.0 to 2.5 mm. perforating electrodes. He also destroys the nutritive vessels. Kaufman and Bennin [243] use surface and penetrating diathermy. They reported on a case with bilateral involvement in which treatment was successful only in the early lesion. Weve [244] discussed this paper and stated that it was a mistake not to operate in early cases, "as the patient will always be affected in both eyes and he will absolutely lose both eyes."

Hallermann [245] electrocoagulated a chorioretinal angioma and later enucleated the eye because of intractable keratitis. Histologic examination showed that the angioma had not been completely destroyed in spite of extensive diathermy. In Callahan's [246] case secondary glaucoma developed and the eye was enucleated.

Reese[247] contends that the lesion of Coats' disease (dark globular retinal detachment in young persons) is essentially a telangiectasis of the retina. He discusses the evolution of the disease from small foci of red globules to the advanced stages. He calls attention to the presence of vascular channels in the inner layers of the retina and demonstrates these with a polyethylene replica. The basement membrane of these channels and also the walls and lumina show a homogeneous red-staining polysaccharide with the Hotchkiss periodic acid stain. In places the channels are occluded. Reese suggests that the progression of the lesion may be due to the formation of this polysaccharide with production of varying degrees of atresia. One patient seems to have had benefit from radiation therapy, but not another. Reese advocates diathermy to the sclera over the lesion if it is small.

Retinal Degenerations

Falls [248,249] discussed the ocular diseases of hereditary origin and reviewed the genetic problems encountered in each of these diseases. Wolter [250] used silver carbonate staining methods to demonstrate beautifully that the peculiar flat cells at the inner surface of the inner limiting membrane of the human retina are astrocytes. Some of these were constantly present in normal aging eyes. These cells hypertrophied and proliferated in retinitis pigmentosa, macular degeneration, and chronic glaucoma. Fuchs [251] described some of the types of drusen of the lamina vitrea that he has seen. His premise is that drusen have a different appearance in the United States from those in Europe and China. He described an interesting case in which the large lesions simulating drusen were probably vesicles between the lamina vitrea and the pigment epithelium. They later disappeared. Pillat [252] showed some of the changes which occur in the retina as a result of the aging process. These include local and diffuse atrophy of the pigment epithelium, loss of sensitivity of the rods and cones, peripheral cystic degeneration, macular cystic degeneration, loss of luster of the internal limiting membrane, retinal concretions, and increased retinal pigmentation.

François, Verriest, and De Rouck [253] summarized the literature on Oguchi's disease and described the 22d non-Japanese case. They classified the disease with the congenital functional anomalies and especially with essential congenital hemeralopia, of

which this seems to be a particular variation. It has no connection with tapetoretinal degeneration in general or with primary degeneration of the retina or retinitis punctata albescens in particular. It is characterized by an adaptation deficiency of the rods. The scotopic components of the electroretinogram are absent. There are defects in photopic and mesopic vision concerning critical flicker fusion and adaptation thresholds, probably due to disturbance of rod function. These authors described a technique [254] for studying the x-wave of the human electroretinogram. This wave was absent in patients who had protanopia, protanomaly, and achromatopsia. The b-wave was not demonstrable, but the x-wave was present in their cases of hemeralopia and Oguchi's disease.

Retinal Degeneration in Animals.—Tansley [255] discussed two types of inherited retinal degeneration found in several experimental animals. One of these is indistinguishable from human recessive retinitis pigmentosa and occurs in dogs, rats, and mice. Chow [256] described the retinas of three chimpanzees. One animal was reared in darkness from birth to 33 months of age; one was kept in darkness from the 8th to the 24th month, and one was reared in the dark from birth to the 7th month except for one and one-half hours of daily diffuse light stimulation. The first two had complete degeneration of the ganglion-cell layer of retina, but the receptive and bipolar layers were normal. The third had a completely normal retina. If the lateral geniculate body of the cat is destroyed, the ipsilateral ganglion cells degenerate but the giant ganglion cells remain normal. Lesions in the superior colliculus have little effect on the retinal ganglion cells.

Pigmentary Degeneration of the Retina.—Lucas [257] described the histologic findings in two cases of retinitis pigmentosa. One is particularly interesting, since there was an enormous thickening of the choroid. This has been noted only twice before in the literature. The other case is the first pathologic report of a case with a dominant mode of inheritance. Campbell and Gebertt [258] treated 14 patients who had retinitis pigmentosa and 5 who had choroideremia with intermedin, a melanophore hormone extracted from the intermediate lobe of the pituitary. They instilled 7 or 8 drops (about 0.45 cc.) into each eye twice weekly. Five of the patients with retinitis pigmentosa had no improvement after 6 months and treatment was then discontinued, but the remainder improved and were treated for 18 to 29 months. About 50% of patients with retinitis pigmentosa had a striking improvement in the visual fields, but the remainder either remained unchanged or declined. No patients with choroideremia improved. Yung-Lin [259] and Turtz [260] each reported a case of unilateral retinitis pigmentosa. Knoll [261] reported on a patient who had pigmentary degeneration of the retina, keratoconus, and glaucoma. Alajmo [262] noted that there has never been a patient reported who had both pigmentary degeneration of the retina and retinal detachment.

Landau and Feinmesser [263] found impaired hearing among 14 of 22 patients with retinitis pigmentosa; 4 patients of 14 had impairment of the caloric response. Four children of two patients with retinitis pigmentosa had normal audiometric tests but had impaired dark adaptation.

Wolter [264] examined the retina of a patient who had far-advanced retinitis pigmentosa and found numerous rosettes of the type seen in retinoblastoma. He demonstrated long glial fibrils in these rosettes. He postulated that the rosettes in this case arose from pathologic glial cells and not from neuroepithelial cells.

François, Verriest, and De Rouck [265] wrote a monograph on the visual function in cases of tapetoretinal degeneration. They included the tests of the photopic and scotopic visual fields, adaptation studies, and electroretinography of patients with various forms of primary pigmentary degeneration of the retina, retinitis punctata albescens, gyrate atrophy, choroideremia, generalized choroidal sclerosis, various forms of macular degeneration, angioid streaks, and chorioret-

initis. Zeavin and Wald [266] studied the visual thresholds and adaptation of rods and cones in normal persons and in patients with early and late retinitis pigmentosa. Iser and Goodman [267] studied flicker photopic electroretinography and stated that both the photopic and the scotopic electroretinogram should be investigated when patients have hereditary retinal degeneration. Dhanda [268] found that patients who suffer from xerosis have a normal electroretinogram if the vitamin A level of the blood is above minimal threshold values but that the electroretinogram is completely extinguished when the level is below this minimum and leads to night blindness. The threshold is near 20 I. U/100 cc. of plasma in children less than 15 years of age, and it is a little higher in adults. Children are more susceptible to the development of night blindness and to loss of electric responses in the retina than are adults.

Sorsby and Savory [269] described two families, both of which had members afflicted with unusual forms of choroidal sclerosis and with variants of choroideremia and retinitis pigmentosa. Westerlund [270] presented data on two families which had choroideremia expressed in the males but in which the females had choroidal pigment disturbance.

Macular Lesions

Horwich and Linfesty [271] and Payne and Crick [272] reported cases of ectopia of the macula, leading to a vertical displacement of the eye. Tower [273] wrote an extensive résumé of the problem of macular-hole formation. In his opinion, vasodilator therapy, particularly retrobulbar injection of tolazoline (Priscoline) or atropine, is effective in causing absorption of macular edema and cysts, thus preventing the formation of a macular hole. De Vincentiis [274] surveyed 57 patients who had retinal holes with or without retinal detachment. He concluded that a hole can be secondary to a detachment, particularly when the detachment comes from peripheral lesions. Sorsby and associates [275] reported on five families who inherited bilateral macular cysts by dominant transmission.

Steinmetz, Ogle, and Rucker [276] traced through eight generations a family that transmitted macular degeneration as an autosomal dominant trait with complete penetrance. Impaired vision began between the 6th and the 12th years and was followed by photophobia and day blindness and later by defective color vision. The macular changes were not visible ophthalmoscopically until the 30th year. Dark adaptation curves showed decreased cone sensitivity with normal rod function. Color vision was deficient, and each affected person had a central scotoma.

Hertzberg [277] had three patients with Tay-Sachs disease in one family; the only Jewish blood came from the paternal great-grandfather. Hoffman [278] reported two cases of Spielmeyer-Vogt juvenile amaurotic family idiocy, discussed the course and pathologic changes, and suggested that the name be changed to "pigmentary retinal lipoid neuronal heredodegeneration."

Goslich [279] saw four cases of juvenile heredodegeneration of the macula (Stargardt type) in three generations and was able with the electroretinogram to differentiate this form definitely from the peripheral tapetodegeneration of primary pigmentary degeneration of the retina. Jacobson, Basar, and Kornzweig [280] found that eyes afflicted with severe disease of the macula showed no response on the electroretinogram when a red stimulus was used, even though the response to white light may have been nearly normal. In their opinion, this phenomenon is due to loss of the photopic mechanism. Wadensten [281] investigated various retinal conditions with flicker electroretinograms. He found that there may be highly defective macular function and yet the flicker electroretinogram may be normal. If the flicker electroretinogram shows defective cone function, central visual acuity is greatly impaired.

Central Serous Retinopathy.—Mitsui and Sakanashi [282] presented a review of the

ophthalmoscopic and biomicroscopic findings among 51 patients with central angiospastic retinopathy. They described three types of lesions: (1) circumscribed serous detachment of the retina (22 cases), (2) circumscribed serofibrinous detachment of the retina (11 cases), and (3) circumscribed retinal edema (7 cases), as well as miscellaneous types (11 cases). They gave excellent descriptions of the various forms that they recognize. In their opinion, tuberculosis is the cause.

Wolkowicz [283] produced subretinal edema (1) by placing a sensitizing dose of horse serum into the suprachoroidal space and then two weeks later injecting horse serum intravenously and (2) by producing light-sensitization of the retina with 1% eosin solution given intravenously and seven days later exposing the eye to a carbon-arc light. He presented two patients who had bilateral central scotomas. One patient had a cecocentral scotoma in one eye and an arcuate scotoma in the other. The author described these cases as central serous retinopathy in which vision was not recovered, although they are in several respects very atypical of the accepted conception of this disease.

Seitz [284] reported on 20 patients with this disease and noted particularly the entoptic phenomena associated with it. He also showed what he considers the characteristic visual field profile—that is, a relative central isle of vision often present in the center of the scotoma. In his opinion, focal infection is very important, and he favors fever therapy. Rusodimos [285] saw seven patients, of whom five recovered under treatment. One recovered spontaneously, and one case ended with degeneration of the macula. Antibiotics and cortisone were ineffective. Sedatives, vasodilators, and vitamins B, D, and E seemed to give the best results. Gordon [286] stated that there was rapid improvement of his patients on 40 mg. of prednisone or prednisolone daily.

Nicholls [287] reported on nine cases in which macular edema appeared in aphakic eyes. Five occurred some months after cataract extraction, and four, at the time of operation. In four cases there was prolapsed vitreous. Several were caused by vitreous detachment, some were central serous retinopathy, and one patient appears to have had senile macular degeneration.

Toxic and Other Injuries to the Retina

Bedell [288] called attention to the forensic value of taking fundus photographs in any cases likely to come to court trial. Norton [289] described an ingenious method of making and later viewing stereophotographs of the retina taken through a binocular ophthalmoscope. Goodside [290] described the appearance and causes of the light reflexes produced by the light from the ophthalmoscope striking the anterior limiting membrane of the retina.

Gregg [291] discussed the effect of maternal rubella on the infant when the infection occurs during the first trimester of pregnancy. He described cataracts, microphthalmos, shallow anterior chamber, changes in the iris, peculiar blotchy pigmentation of the macula and perimacular region with little or no visual defect, nyastagmus, hydrophthalmia, and corneal opacities.

Siegert [292] found the following changes in the eyes of recently returned malnourished long-term prisoners of war of the U.S.S.R.: stippled lesions of the macula, due to capillary dysfunction, and local destruction of the macula. He considered that the cases of retrobulbar neuritis resulted from avitaminosis, toxins, infections, and from direct photogenic and radiogenic influences leading to so-called camp-amblyopia. A high percentagee of prisoners had subnormal adaptation. This was observed particularly among those who had dry or moist lipodystrophy but also among otherwise healthy long-term prisoners. Xerosis of the conjunctiva and keratomalacia were rare.

Radiant and Solar Energy.—Noell and Cibis [293] studied retinal degeneration in rabbits and monkeys resulting from intravenous administration of iodoacetate and from high-intensity roentgen irradiation of the whole head or of one eye. The rod cells degenerated rapidly, but the inner retinal layers were hardly affected. Rugh and Wolff [294]

exposed pregnant mice to whole body x-irradiation at 12½ and 13½ days of gestation (at the time when the fetal eyes are actively differentiating) with doses ranging from 50 to 300 r. They then studied these eyes histologically at varying intervals and found a high degree of initial destruction of the retina but rapid functional restitution. Brown, Cibis, and Pickering [295] exposed monkeys to Co^{60} gamma radiation, which caused severe iridocyclitis, retinal edema, papilledema, severe hypotonia, and, in some cases, punctate and flame-shaped hemorrhages. Histologic abnormalities consisted chiefly of pyknosis of rod nuclei (apparent as early as two hours after irradiation) and degenerative sequelae in the outer nuclear and bacillary layers. Shields protected the eyes completely against such effects. Newell, Harper, and Köistenen [296] attached yttrium ^{90} pellets to the sclera. This material produces pure β-rays. The initial reaction was one of acute necrosis of sclera, choroid, and retina. There was necrosis even of the participating polymorphonuclear cells. Sometimes the sclera ruptured. Healing began after two weeks. No cataracts were noted. Retinal destruction was severer than choroidal destruction.

Burmeister [297] treated patients with the "radartherm," which radiates power of 25 watts in the wavelength range of 12 cm. He claimed distinct improvement in several types of ocular diseases.

Jonquères and de Saint-Martin [298] reported chorioretinitis caused by electrocution with a high tension wire.

Byrnes and associates [299] and Rose and associates [300] reported data on chorioretinal lesions produced by the atomic bomb. Chambers [301] thought that cortisone systemically was of value to curtail the inflammatory reaction of such burns.

Das, Nirankari, and Chaddah [302] reported on 37 patients who sustained macular burns during a solar eclipse. Eighty-four per cent of these occurred among the group 11 to 30 years of age. Myopic eyes without proper glasses sustained the least damage, and hypermetropic eyes suffered most. The patients with the greatest subjective symptoms sustained the least permanent damage. The final outcome ranged from normal maculas with good vision to atrophic lesions causing gross permanent visual defects.

Meyerratken [303] reported on 12 eclipse burns. The highest degree of visual impairment was 20/80 shortly after the injury, and after six months the worst visual defect was 20/28. Gebertt [304] treated 55 such burns with retrobulbar injection of 0.25 mg. carbachol. Thirty-nine patients improved 2 to 30 minutes after the injection, but the remainder received no help. The 39 received a second injection two or three days later. Münchow [305] devised a simplified Landolt-Amsler grid for demonstrating these scotomas. Meyer-Schwickerath and associates [306] photocoagulated the chorioretinal tissues of rabbits and found smaller scars when the rabbits received phenylbutazone (Butazolidin) intramuscularly than when they did not receive it.

Chemicals.—Dische [307] reviewed the considerable literature on the physiologic chemistry of the eye for 1955 and discussed that which pertained to the retina. Apter and Pfeiffer [308] ascribed the visual hallucinations caused by mescaline and lysergic-acid diethylamine tartrate (LSD-25) to retinal damage. This is predicated on the onset of visual hallucinations which arise in the cat at the same time as spontaneous action potentials in the electroretinogram after one of these drugs is given. Potts, who discussed this paper, had no such results in similar investigations.

In the opinion of Leplat and Gerebtzoff, [309] epinephrine and arterenol are located in the sensory cells of the retina and acetylcholinesterase is located in the inner plexiform layer. They consider the rods and cones adrenergic and the ganglion cells and bipolar cells cholinergic. Kornblueth and Ben-Shlomo [310] reported that methyl alcohol, quinine, sodium cacodylate, formaldehyde, acidosis, physostigmine, isoflurophate, acetazoleamide ethionine, sodium iodate or azide, and aminopterin had no effect on the normal utilization of glucose by the rat retina.

Iodoacetic acid caused a 30% inhibition of the rat retina, but brain and diaphragm were not affected.

Nishi [311] sensitized rabbits to white of egg. Injection later into the anterior chamber and vitreous caused acute iridocyclitis. Injected into the retrobulbar space, it caused retrobulbar neuritis and even choroiditis.

Optic Nerve

Carroll and associates [312] conducted a symposium on "Diseases of the Optic Nerve." Since this is a very complete and excellent exposition of the subject, no attempt can be made here to abstract the wealth of information contained in it, and it should be read in its entirety.

Dubois-Poulsen [313] described the production of a Bjerrum scotoma by injecting 5% formalin into a Cysticercus cyst which lay on the outer aspect of the optic nerve immediately behind the globe. He produced Rönne's step by dazzling the central retina. He ascribes the step to an unequal fall in sensation of the upper and lower retinal quadrants, whereas he considers the Bjerrum scotoma as of retrobulbar origin. Trantas [314] investigated the photosensitivity of the retina in various nerve and retinal affections, using a tiny bright spot of light or a tiny dark spot inserted into the beam of the ophthalmoscope. By alternating these two stimuli, the author tested the retina in the manner of testing skin sensation with a pin.

François and Neetens,[315] in their third paper on the subject, demonstrated by serial sections the characteristic pattern of vascularization of the several divisions of the optic nerve. The central artery and its collaterals serve only the retina and do not send branches to the optic nerve. With the silver carbonate stain Wolter [316] demonstrated the various pathologic changes in the retina and optic nerve. The article deserves reading in its entirety.

Niedermeier [317] used intradural injection and vital staining in experimental animals to show that a rise of intracranial pressure disturbs the vascular permeability in the region of the lamina cribrosa. In his opinion, the mechanism of papilledema depends both on mechanical and on autonomic factors. Minton [318] presented a 9-year-old boy who had proptosis and blepharoptosis of the left eye, venous dilatation of the lids and cheek, a hemangioblastoma below the left disk, and an arteriovenous malformation in the distribution of the left middle cerebral artery. Episodes of subarachnoid hemorrhage continued even after ligation of the left common and internal carotid arteries.

Wagener [319] reviewed the recent literature pertaining to loss of vision from exophthalmos of endocrine origin. He presented the evidence pointing toward a separate hormone as the cause of the exophthalmos, a hormone distinct from the thyroid-stimulating hormone. He urged orbital decompression when evidence of optic nerve involvement appears, and advocated removal of the roof and lateral wall of the orbit. Hedges and Scheie [320] reported six such patients with field defects and thought that the defects were due to impaired circulation of the optic nerve caused by increased orbital pressure.

Congenital Anomalies.—Rizzoli [321] described a unique case in which one eye of the patient had a double optic disk, one disk above the other. The lower disk was only one-third as large as the upper. Vision was normal. Vauthier and Zanen [322] presented five cases with congenital holes in the optic disk. They showed the associated visual field defects. Sena, Cerboni, and Kutyn [323] reported colloid bodies in the optic disks of a mother and son. There were marked defects in the visual fields of the 17-year-old son but only mild defects in those of the mother. La Rocca [324] reported a patient who in one eye had a partial coloboma of the optic disk and choroid and in the other eye had pseudopapillitis. This patient had a cavernous angioma of the face. The case is presented in support of the hypothesis that colobomas are of vascular origin. Marquart [325] reported on 18 cases in which a diagnosis of choked disks was not substantiated by further investigation. They

were then rediagnosed as pseudopapilledema due to refractive error, formation of drusen, or vascular disease.

Traumatic Lesions.—Kirichenko [326] saw two cases of traumatic evulsion of the optic disk. There was little external trauma, but there was extensive hemorrhage near the optic disk. Landolt [327] presented 19 patients who had unilateral lesions of the optic nerve following trauma to the skull. Three-fourths of them had fractures of the lesser wing of the sphenoid. In all cases the injury was to the front half of the skull. Pupillary function usually was impaired. Since there was a high incidence of permanent blindness, the author advised early decompression. He assumed that a hidden fracture can produce compression of the nerve either by hemorrhage or by edema. Martelli and Strazzi [328] expressed the same opinion.

Optic Neuritis.—On the basis of measurements of the critical fusion frequency in the area of the visual field corresponding to the scotoma of patients with retrobulbar neuritis, Kurachi and Yonemura [329] reached the questionable conclusion that the site of the block may be in the neuronal network of the bipolar-cell layer and not in the nerve fibers behind the globe. Steinmetz and Kearns [330] emphasized the value of the H-R-R pseudoisochromatic test for defective color vision as an aid in the detection of very minimal visual loss from a previous attack of retrobulbar neuritis.

Victoria, [331] Ros Pena, [332] and Velásquez [333] reported on families whose members were afflicted with hereditary optic atrophy. Velásquez investigated a Negro family of 21 members, among whom 10 members in three generations had the disease transmitted as a sex-linked dominant.

Glick and Mumford [334] reported on a patient who had quinine amblyopia and who remained blind for 40 hours. She had an immediate return of vision after stellate ganglion block. In the opinion of the authors, this result supports the view that vasospasm is an important factor in the causation of this condition. They think also that this case indicates that stellate block should be used in treating central vein thrombosis and central artery embolism.

Gilger, Potts, and Farkas [335] used monkeys to reach the conclusion that large doses of ethyl alcohol inhibit the disastrous effects of methyl alcohol poisoning. They recommended early therapy with 4½ oz. (135 cc.) of 100 proof whisky N. F. followed every four hours by 3 oz. (90 cc.), and at the same time the acidosis should be treated with base. Fornaro [336] studied the gastric function, blood, and hepatic activity of patients with tobacco-alcohol amblyopia and decided that the histamine-resistant achylia observed among 10 of 12 patients was probably responsible for the complete deficiency of blood-regulating, vitamin, and nutritional factors, which in turn caused anemia and amblyopia. Guttmann-Friedmann [337] described severe and permanent impairment of vision resulting from bilateral optic neuritis following the bite of a venomous snake.

Marin Amat [338] made an analysis of the ocular complications encountered among 100 patients who had tuberculous meningitis. Abnormalities of the pupils were found in 55%, and all had lesions of the fundi; 29% had papilloretinal edema; 19% had papillitis, 12% had intense papillitis; 12% had postneuritic optic atrophy, and the remainder had miscellaneous involvement. Mooney [339] reported 65 such patients, of whom 80% survived. Forty-seven (72%) had one or multiple ocular lesions, which included papilledema (26%), choroidal tubercles (25%), pallor of the disks (20%), ocular palsies (15.5%), retrobulbar neuritis (two cases), and homonymous hemianopsia (one case). Mooney emphasized the importance of the tubercle as an index of the efficacy of treatment. He advocated early decompression to save vision and life when choked disks appear. In eight cases exploration was performed because of pallor of the disks. In all of these, large soft or calcified adhesions were removed from the optic nerves and chiasm; five patients recovered vision and three did not. The recoveries were at-

tributed to prompt surgical intervention; in cases of failure to recover, the operation was considered to have been performed too late. In one interesting case there was apparently an intramedullary tubercle of the intracranial portion of the left optic nerve.

Stagni [340] reported good results of treatment in 43 patients with retrobulbar neuritis to whom he administered nicotinic acid by retrobulbar injection. Brihaye-van Geertruyden [341] claimed that, although cortisone given orally was ineffective in restoring vision to her patient, retrobulbar cortisone was effective in her case when used after the eighth day of the disease. Wagener and Horton [342] reported treatment of patients who had optic nerve, retinal, and choroidal lesions with intravenous histamine given over prolonged periods. These patients were all persons who had been told that no further improvement could be expected spontaneously or from other treatment. Of those with optic nerve lesions, 42 eyes (74%) improved; of those with chorioretinitis, 11 (69%) improved, and of those with chorioretinal degeneration, 4 (18%) had some improvement.

Optic Atrophy.—Ferreira [343] reviewed and classified the varieties of optic atropy. Le Grand and Verlaeken [344] reported on four cases of visual disorder following distant hemorrhage. These patients had initially ischemia of the retina and optic disk and later the usual optic nerve atrophy. Takahashi [345] injected rabbits with vasopressin (Pitressin) and produced optic atrophy, followed by ataxia, mydriasis, and pupillary areflexia. The author demonstrated demyelinization in the central nervous system associated with vascular narrowing and formation of thrombi. He mentioned the analogy to multiple sclerosis. Klauder [346] called attention to the gradual and progressive decline in the numbers of patients afflicted with ocular syphilis and stated that at the present time a new case of optic atrophy is rarely seen.

Cutler and Blatt [347] described two cases of lethal midline granuloma (Wegener's granulomatosis). This may invade the orbit and cause papilledema and optic atrophy on one or both sides and may produce proptosis or ophthalmoplegia or may actually invade the ocular coats. Gross [348] showed necropsy specimens of cases of cranial dysostosis (turricephaly) demonstrating that one cause of the optic atrophy is the upward traction exerted on the optic nerves as the brain is pulled upward by its growth.

Hobbs [349] and Rychener and Murphey [350] discussed the ocular manifestations of periorbital fibrous dysplasia. This lesion frequently produces exophthalmos, compression of the optic nerve or chiasm, optic atrophy, and papilledema.

Matteucci and Kluzer [351] discussed 10 cases of optic nerve compression and made the rather questionable statement that the site of involvement of the optic nerve is difficult to determine in such lesions. Wolter and Liss [352] reported on two cases in which a tumor compressed the optic nerve. They stained the excised optic nerves with a modified Hortega silver stain and found first an irritation of the astrocytes with reversible damage to the nerve fibers but later a hypertrophy and proliferation of the astrocytes with irreversible nerve damage. Finally, the astrocytes break down and there is connective tissue proliferation. Frezzotti [353] described a patient who had a Foster Kennedy syndrome. The tumor was found to be a sphenoid ridge meningioma, but it was situated on the side of the papilledema instead of on the side of the optic atrophy.

Tumors of the Optic Nerve.—Walsh [354] gave a very detailed and interesting report of highlights of various manifestations of tumors affecting the optic nerves and chiasm. The article should be read, since it cannot be well abstracted. Taveras, Mount, and Wood [355] advocated radiation therapy for gliomas of the optic nerve and chiasm in dosage of 800γ to 1,500γ repeated two or three times during the early months following diagnosis. If the tumor is confined to one optic nerve and can be completely removed surgically, this is the procedure of

choice and should be followed by irradiation. All other patients should have only irradiation. Results have been surprisingly good. About half had an arrest of the visual loss, and some patients have improved. Hanbery [356] pointed out that 90% of optic nerve gliomas occur before the age of 20 years. He emphasized the frequency of association with von Recklinghausen's neurofibromatosis. He stated that prognosis is excellent if all of the lesion is removed at the first operation. Razumikhina [357] reported on a meningioma of the optic disk, which had caused loss of vision 14 years before and beginning proptosis 12 years before. It proved to have originated in the endothelial cells of the nerve sheath.

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REFERENCES

1. Wagener, H. P.: Diseases of the Retina and Optic Nerve, A. M. A. Arch. Ophth. 55:699-746 (May) 1956.

2. Duke-Elder, S., and others: Retrolental Fibroplasia in the United Kingdom: A Report to the Medical Research Council by Their Conference on Retrolental Fibroplasia, Brit. M. J. 2:78-82 (July 9) 1955.

3. Boyd, J. T., and Hirst, K. M.: Incidence of Retrolental Fibroplasia in England and Wales in 1951, Brit. M. J. 2:83-85 (July 9) 1955.

4. Guy, L. P.; Lanman, J. T., and Dancis, J.: The Possibility of Total Elimination of Retrolental Fibroplasia by Oxygen Restriction, Pediatrics 17:247-249 (Feb.) 1956.

5. Kinsey, V. E.; Jacobus, J. T., and Hemphill, F. M.: Retrolental Fibroplasia: Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen, A. M. A. Arch. Ophth. 56:481-543 (Oct.) 1956.

6. Ashton, N.; Gordon, H. H.; Szewczyk, T.; Bedrossian, R. H.; Carmichael, P.; Ritter, J. A., and Locke, J. C.: Panel Discussion: The Prevention and Management of Retrolental Fibroplasia with Emphasis on the Role of Oxygen in Its Pathogenesis, Acta XVII Conc. Ophth. (1954) 1:1-25, 1955.

7. Retrolental Fibroplasia, Editorial, Brit. M. J. 2:110-111 (July 9) 1955.

8. Hollenhorst, R. W.: Oxygen Therapy in the Premature Infant as a Cause of Retrolental Fibroplasia, Minnesota Med. 39:91-93 (Feb.) 1956.

9. Castrén, J.: The Significance of Prematurity on the Eye, with Reference to Retrolental Fibroplasia, Acta ophth., Supp. 44, pp. 1-109, 1955.

10. Greenhouse, J. M., and Szewczyk, T.: Skin Hemangioma and Retrolental Fibroplasia, A. M. A. Arch. Dermat. & Syph. 73:568-571 (June) 1956.

11. Melanowski, W. H., and Kobuszowski, M.: Deux cas de fibroplasie rétrolentale: Contribution à la pathogénie d'hydrophthalmie, Bull. et mém. Soc. franç. opht. 68:238 (May) 1955.

12. Hellström, B. E.: Experimental Approach to the Pathogenesis of Retrolental Fibroplasia, Uppsala, Sweden, Almqvist & Wiksells Boktryckeri, 1956.

13. Gyllensten, L. J., and Hellström, B. E.: Experimental Approach to the Pathogenesis of Retrolental Fibroplasia: IV. The Effects of Gradual and of Rapid Transfer from Concentrated Oxygen to Normal Air on the Oxygen-Induced Changes in the Eyes of Young Mice, Am. J. Ophth. 41:619-627 (April) 1956.

14. Hellström, B. E.: Experimental Approach to the Pathogenesis of Retrolental Fibroplasia: V. The Influence of the State of Nutrition on Oxygen-Induced Changes in the Mouse Eye, Acta pædiat. 45:43-57 (Jan.) 1956.

15. Hellström, B. E.: Experimental Approach to the Pathogenesis of Retrolental Fibroplasia: VI. The Influence of the Oxygen Concentration on the Oxygen-Induced Changes in the Mouse Eye, Acta pædiat. 45:295-308 (May) 1956.

16. Hellström, B. E.: Experimental Approach to the Pathogenesis of Retrolental Fibroplasia: VII. Effect of Oxygen Exposure on the Electroretinogram in Kittens, A. M. A. Arch. Ophth. 55:211-220 (Feb.) 1956.

17. Habegger, H.; Philbrook, F. R.; Curley, F. J., and Ingalls, T. H.: Retinopathy of Immaturity: In the Newborn Mouse After Exposure to Oxygen Imbalances, Am. J. Ophth. 42:377-392 (Sept.)1956.

18. Michaelson, I. C.: Unilateral Budding in New Vessel Formation in the Eye, Brit. J. Ophth. 40:36-39 (Jan.) 1956.

19. Mercier, M. A.: Essais d'utilisation de la clorpromazine dans la rétinopathie des prématures, Bull. et mém. Soc. franç. opht. 68:231-236 (May) 1955.

20. Kozuchowska, J.: Retinal Hemorrhages in Newborn, Post. okul. 1:167-177, 1954; abstracted, Am. J. Ophth. 41:730 (April) 1956.

21. Humblet, M.; Cavrot, E., and Richard, J.: L'Hémorragie rétinienne du nouveau-né à terme, Bull. Soc. belge opht. 110:137-140 (June) 1955.

22. McNeil, N. L.: Some Ocular Manifestations of Prematurity, Brit. J. Ophth. 40:24-29 (Jan.) 1956.

23. Birge, H. L.: Myopia Caused by Prematurity, Am. J. Ophth. 41:292-298 (Feb.) 1956; Tr. Am. Ophth. Soc. 53:219-230, 1955.

24. Tassman, I. S.: Ocular Changes in Diabetes Mellitus, Survey Ophth. 1:299-314 (Aug.) 1956.

25. Urrutia, D.; Bitran, D.; Bonnefoy, J., and Pinto, C.: La Retinopatía diabética, Arch. chilen. oftal. 12:153-161 (Aug.-Dec.) 1955.

26. Miratynska-Rusinowa, E., and Lisiecka-Adamska: Diabetic Retinopathy, Klin. oczna 25: 37-48 1955; abstracted, Am. J. Ophth. 42:182 (July) 1956.

27. Dollfus, M. A.: Examen ophtalmologique de 1300 diabétiques, Acta XVII Conc. Ophth. (1954) 1:119-127, 1955.

28. Lundbaek, K.: Diabetic Retinopathy in Newly Diagnosed Diabetes Mellitus, Acta med. scandinav. 152:53-60 (July 29) 1955.

29. Givner, I.: Ocular Observations on the Diabetic Patient, Am. J. Ophth. 41:285-288 (Feb.) 1956.

30. Kornerup, T.: The Visual Prognosis in Diabetes Mellitus, Acta ophth. 34:201-207, 1956.

31. Fischer, F.: Papillenöden bei diabetischer Retinopathie, von Graefes Arch. Ophth. 157:201-206, 1955.

32. Quiroz, J. A., and Sauter, A.: La Angioesclerosis retiniana en enfermos diabéticos no hipertensos, Acta XVII Conc. Ophth. (1954) 1: 309-315, 1955.

33. Volk, D.: Dissimilarity of Retinal Microaneurysm and Glomerular Nodule in Diabetes, A. M. A. Arch. Ophth. 56:188-193 (Aug.) 1956.

34. Kornerup, T.: Capillary Fragility and Diabetic Retinopathy, Acta ophth. 33:583-598, 1955.

35. Lerman, S., and Pogell, B. M.: Serum Protein Changes in Diabetic Retinopathy, abstracted, Am. J. Ophth. 42:129 (July) 1956.

36. Morone, G.: Glucosamine in the Serum of Patients with Diabetic Retinopathy, Gior. ital. oftal. 8:365-373 (Sept.-Oct.) 1955; abstracted, Am. J. Ophth. 42:163 (July) 1956.

37. Morone, G.: The Role of the Mucopolysaccharides in Diabetic Retinopathy, Rass. ital. ottal. 24:161-165 (May-June) 1955; abstracted, Am. J. Ophth. 41:350 (Feb.) 1956.

38. Harris, J. E., and Lerner, A. B.: The Excretion of Melanocyte-Stimulating Hormone by Patients with Certain Ocular Disorders, abstracted, Am. J. Ophth. 41:537-538 (March) 1956.

39. De Conciliis, U.: The Blood-Aqueous Barrier, the Ocular Fundus and the Retinal Respiration in Acute and Chronic Hypoglycemia, Arch. ottal. 60:31-44 (Jan.-Feb.) 1956; abstracted, Am. J. Ophth. 42:512 (Sept.) 1956.

40. Fischer, F.: Die Therapiefrage der diabetischen Retinopathie, von Graefes Arch. Ophth. 157: 495-505, 1956.

41. Lijó Paviá, J.: Macula-mejoría de lesiones degenerativas tratadas con cortisona, Rev. otoneuro-oftal. 30:85-88 (May-June) 1955.

42. Schimek, R. A.: Hypophysectomy for Diabetic Retinopathy: A Preliminary Report, A. M. A. Arch. Ophth. 56:416-425 (Sept.) 1956.

43. Malins, J. M.: Adrenalectomy for Vascular Disease of Diabetes, Lancet 1:530-534 (April 28) 1956.

44. Elwyn, H.: The Changes in the Fundus of the Eye in Arterial Hypertension, A .M. A. Arch. Ophth. 55:3-8 (Jan.) 1956.

45. Birge, H. L.: Vascular Disease: From the Ophthalmological Standpoint, Connecticut M. J. 19:857-863 (Nov.) 1955.

46. Sautter, H.: Die Arteriosklerose des Augenhintergrunds, Klin. Monatsbl. Augenh. 127:641-657, 1955.

47. Weigelin, E.: Statistische Untersuchung der Augenhintergrundsveränderungen bei Hypertonie, Acta XVII Conc. Ophth. (1954) 1:585-595, 1955.

48. Wagener, H. P.: Discussion, Acta XVII Conc. Ophth. (1954) 1:594-595, 1955.

49. Lijó Paviá, J.: Arteriosclerosis, Hypertension, and Retinopathy: General and Ocular Improvement with Hormonal Treatment, Am. J. Ophth. 41:85-92 (Jan.) 1956.

50. Miller, H. A., and Audoueineix, E.: Diastolic Retinal Pressure: Its Value and Significance in Vascular Hypertension, Tr. Ophth. Soc. U. Kingdom. 75:391-403, 1955.

51. Kunitomo, N.; Inoue, Y.; Takeuchi, E., and Chigusa, M.: Relationship Between Hypertension and Blood Vessels of the Eye by Slit-Lamp Examination, Acta XVII Conc. Ophth. (1954) 1:341-347, 1955.

52. Sasamoto, M.: Relation of Acetylcholine Test to Blood Pressure and Fundus Findings in Hypertensive Patients, Acta Soc. ophth. japon. 59:1371-1382 (Sept.) 1955; abstracted, Am. J. Ophth. 41:740 (April) 1956.

53. Winter, S. T.; Laron, Z., and Michaelson, I. C.: Renal and Vascular Disturbances in a Case of Thallium Poisoning, Arch. Dis. Childhood 29:443-446 (Oct.) 1954.

54. Hagans, J. A.; Brust, A. A., and Ferris, E. B.: Malignant Hypertension: Influence of Retinopathy, Uremia and Underlying Renal Disease on Mortality and Survival Time, Am. J. Med. 19:141 (July) 1955.

55. Kirby, T. J., Jr., and Hollenhorst, R. W.: Asymmetric Hypertensive Retinal Changes After Ligation of the Internal Carotid Artery, Acta XVII Conc. Ophth. (1954) 1:335-338, 1955.

56. Newborg, B., and Kempner, W.: Analysis of One Hundred Seventy-Seven Cases of Hypertensive Vascular Disease with Papilledema: One Hundred Twenty-Six Patients Treated with Rice Diet, Am. J. Med. 19:33-47 (July) 1955.

57. Volkova, M.: The Use of Novocaine Block in Hypertension with Fundus Changes, Vestnik oftal. 34:17-21 (March-April) 1955; abstracted, Am. J. Ophth. 41:907 (May) 1956.

58. Turner, R. H., and Bowers, C. Y.: The Minute Blood Vessels in Disease, editorial, Am. J. Med. 18:169-171 (Feb.) 1955.

59. Wybar, K. C.: Anastomoses Between the Retinal and Ciliary Arterial Circulations, Brit. J. Ophth. 40:65-81 (Feb.) 1956.

60. Wybar, K. C.: Anastomoses Between the Uveal and Retinal Circulations and Their Significance in Vascular Occlusion, Acta XVII Conc. Ophth. (1954) 1:294-301, 1955.

61. Shea, M.: Carotid-Ophthalmic Anastomoses: Frequency of External Carotid and Ophthalmic Artery Anastomoses, Brit. J. Ophth. 40:497-501 (Aug.) 1956.

62. Keeney, A. H., and Barlow, F. D.: Histologic Methods in the Study of Retinal Vascular Patterns: In the Albino Rat, Am. J. Ophth. 42:554-560 (Oct., Pt. 1) 1956.

63. Bettman, J. W., and Fellows, V. G., Jr.: A Technique for the Determination of Blood-Volume Changes: In the Choroid and Retina by the Use of Radioactive Phosphorus, Am. J. Ophth. 42:161-166 (Oct. Pt. 2) 1956.

64. Wudka, E., and Leopold, I. H.: Experimental Studies of the Choroidal Vessels: I. Historical Survey; II. Methods and Material of Investigation; III. Anatomical Observations, A. M. A. Arch. Ophth. 55:605-632 (May) 1956.

65. Wudka, E., and Leopold, I. H.: Experimental Studies of the Choroidal Vessels: IV. Pharmacologic Observations, A. M. A. Arch. Ophth. 55:857-885 (June) 1956.

66. Staenglen, K.: Über Probleme und tierexperimentelle Ergebnisse der retinalen Hyperämiebehandlung, von Graefes Arch. Ophth. 157: 559-591, 1956.

67. Wethmar, A.: Über den Einfluss gefässerweiternder Mittel auf die Gefässe der Netzhaut, Klin. Monatsbl. Augenh. 129:231-252, 1956.

68. Zahn, K., and Simková, M.: Die Wirkung von l-Nor-Adrenalin auf den retinalen Blutkreislauf, Ophthalmologica 131:65-71 (Jan.) 1956.

69. Mikuni, S.: Blood Pressure of Retinal Artery in Some Fundus Diseases: I.-V., Acta Soc. ophth. japon. 59:1359-1364; 1577-1603; 1645-1657; 1748-1753 (Sept.-Oct.-Nov.) 1955; abstracted, Am. J. Ophth. 41:587-588 (March) 1956.

70. François, J., and Verriest, G.: La Campimétrie à l'obscur dans les affections vasculaires de la rétine, Bull. Soc. belge opht. 111:463-494 (Nov.) 1955; Ann. ocul. 189:549-580 (June) 1956.

71. Dobree, J. H.: Calibre Changes in Retinal Vessels Occurring in Raised Ocular Tension: Circulatory Compensation in Chronic Glaucoma, Brit. J. Ophth. 40:1-13 (Jan.) 1956.

72. Abboud, I.: Obstruction of the Retinal Arteries, Bull. Ophth. Soc. Egypt 48:169-172, 1955.

73. Krasnov, M.; Kritchewskaya, E.; Shakhnowich, S.; Shulpina, N., and Gelfman, A.: Dicumarin in the Thrombo-Embolic Syndrome of the Retinal Vessels, Vestnik oftal. 1:3-8 (Jan.-Feb.) 1956; abstracted, Am. J. Ophth. 41: 1104-1105 (June) 1956.

74. Patz, A.: Oxygen Inhalation in Retinal Arterial Occlusion: A Preliminary Report, Am. J. Ophth. 40:789-795 (Dec.) 1955.

75. Heer, G.: Central Scotoma in a Case of Occlusion of a Branch of the Central Retinal Artery, Rass. ital. ottal. 24:285-293 (July-Aug.) 1955; abstracted, Am. J. Ophth. 41:586-587 (March) 1956.

76. Bellavia, M.: Jensen's Chorioretinitis (Clinical Case), Arch. ottal. 59:377-391 (Sept.-Oct.) 1955; abstracted, Am. J. Ophth. 41:348-349 (Feb.) 1956.

77. Klien, B. A.: Jensen's Juxtapapillary Retinopathy (Idiopathic Focal Retinal Arteriolitis), Am. J. Ophth. 42:9-14 (July) 1956.

78. Kearns, T. P.: Fat Embolism of the Retina: Demonstrated by a Flat Retinal Preparation, Am. J. Ophth. 41:1-2 (Jan.) 1956.

79. Pünder, H., and Schmidt, K-H.: Zur Fettembolie mit Augenbeteiligung, Klin. Monatsbl. Augenh. 127:427-431, 1955.

80. Schenk, H.: Über das Auftreten einer Retinopathia traumatica Purtscher nach Unterbindung der Arteria carotis communis, Klin. Monatsbl. Augenh. 127:669-676, 1955.

81. Venturi, G.: Temporal Arteritis (Case Report), Arch. ottal. 59:453-488 (Nov.-Dec.) 1955; abstracted, Am. J. Ophth. 41:741 (April) 1956.

82. Bennett, G.: Cortisone Therapy of Visual Loss in Temporal Arteritis, Brit. J. Ophth. 40: 430-433 (July) 1956.

83. Klien, B. A., and Olwin, J. H.: A Survey of the Pathogenesis of Retinal Venous Occlusion: Emphasis upon Choice of Therapy and an Analysis of the Therapeutic Results in 53 Patients, A. M. A. Arch. Ophth. 56:207-247 (Aug.) 1956.

84. Barsky, D.: Central Retinal Vein Occlusion Treated with Anticoagulant and Steroid Therapy: Case Report and Discussion, Henry Ford Hosp. Bull. 4:98-101 (June) 1956.

85. Morgan, O. G.: Some Aspects of Thrombosis of the Retinal Vein and Its Treatment, Tr. Ophth. Soc. U. Kingdom 75:3-24, 1955.

86. Montagne, F.: Utilisation d'un nouveau dérivé de la coumarine dans les thromboses veineuses de la rétine, Arch. opht. 15:850-853 (Nov.-Dec.) 1955.

87. Mikuni, M., and Ibaraki, Y.: Klinische Erfahrungen mit Padutin (Bayer) bei der Netzhaut-Venenthrombose, Klin. Monatsbl. Augenh. 128:323-332, 1956.

88. Cuendet, J. F.; Miescher, P.; Ritter, O., and Sicard, G.: La Thrombose récidivante en ophtalmologie, Bull. et mém. Soc. franç. opht. 68:254-259 (May) 1955.

89. Smith, R.: Concerning Glaucoma and Retinal Venous Occlusion, Tr. Ophth. Soc. U. Kingdom. 75:265-279, 1955.

90. Smith, R.: Thrombotic Glaucoma: A Clinico-Pathological Study, Acta XVII Conc. Ophth. (1954) 2:1164-1174, 1955.

91. Karpe, G., and Uchermann, A.: The Clinical Electroretinogram: VII. The Electroretinogram in Circulatory Disturbances of the Retina, Acta ophth. 33:493-516, 1955.

92. Henkes, H. E.: Some Aspects of Electroretinography in General Hypertension and Arteriosclerosis, Acta XVII Conc. Ophth. (1954) 1:317-323, 1955.

93. Hogan, M. J.: Ocular Toxoplasmosis: Clinical and Laboratory Diagnosis; Evaluation of Immunologic Tests; Treatment, A. M. A. Arch. Ophth. 55:333-345 (March) 1956.

94. Sabin, A. B.: Human Toxoplasmosis: With Special Reference to Intraocular Inflammation; A Critical Review; The Sixth William Hamlin Wilder Memorial Lecture, Am. J. Ophth. 41:600-606 (April) 1956.

95. Burnham, C. J., and Beuerman, V. A.: Toxoplasmic Uveitis, Am. J. Ophth. 42:217-227 (Aug.) 1956.

96. Swan, C., and French, E.: A Case of Toxoplasmosis, M. J. Australia. 1:1009-1011 (June 16) 1956.

97. François, J.; Rabaey, M.; Evens, L., and DeVos, E.: Étude histo-pathologique d'une rétinite de Coats probablement toxoplasmique, Bull. Soc. belge opht. 111:448-463 (Nov.) 1955.

98. Straub, W.: Exogene und endogene Toxoplasmose des Auges im Tierversuch, Acta XVII Conc. Ophth. (1954) 3:1729-1737, 1955.

99. Straub, W.: Toxoplasmose des Auges: Experimentelle Untersuchungen über die Art und den Verlauf der Erkrankung bei Kaninchen und Meerschweinchen, Ophthalmologica, Supp. 41, pp. 1-80, 1955.

100. Arribas, N. P., and Schlaegel, T. F., Jr.: Experimental Toxoplasmosis in the Rabbit: I. Natural Course After Intraocular Injection, Am. J. Ophth. 41:1069-1070 (June) 1956.

101. Jacobs, L.; Hart, W. M.; Ryan, R. W., and Cook, M. K.: The Production of Experimental Ocular Toxoplasmosis in Rabbits, Acta XVII Conc. Ophth. (1954) 3:1946-1951, 1955.

102. Hogan, M. J.; Zweigart, Phyllis A., and Lewis, A.: Persistence of Toxoplasma Gondii in Ocular Tissues, Am. J. Ophth. 42:84-88 (Oct., Pt. 2) 1956.

103. O'Connor, G. R.: The Agar-Diffusion Technique as Applied to the Detection of Anti-Toxoplasma Precipitins in Aqueous Humor, abstracted, Am. J. Ophth. 42:131-132 (July) 1956.

104. Frenkel, J. K.: Chorioretinitis Associated with Positive Tests for Toxoplasmosis, Acta XVII Conc. Ophth. (1954) 3:1965-1972, 1955.

105. Bennett, G.: Uveitis: A Clinical and Statistical Survey, Brit. J. Ophth. 39:727-742 (Dec.) 1955.

106. Edling, N. P. G.: The Roentgenological Findings of the Nasal Sinuses in Uveitis, Acta ophth. 33:627-630, 1955.

107. Kimura, H.: A Fundamental Study on Tuberculosis of the Eyes: IV.-V., Acta Soc. ophth. japon. 60:363-380 (May) 1956.

108. Dufour, R.: Lésions uvéales et vasculaires rétiniennes précoces dans l'infection tuberculeuse, Ophthalmologica, Supp. 44, pp. 1-53, 1956.

109. Kraffel, G.: Beitrag zur Chorioretinitis striata, Klin. Monatsbl. Augenh. 127:664-669, 1955.

110. Boase, A. J.: Coenurus Cyst of the Eye, Brit. J. Ophth. 40:183-185 (March) 1956.

111. Couran, O. F., and Waddy, B. B.: Effect of Antrypol Treatment of Blindness Due to Onchocerciasis, J. Trop. Med. 59:53-56 (March) 1956; abstracted, Am. J. Ophth. 42:185 (July) 1956.

112. Somerset, E. J., and Sen, N. R.: Leprosy Lesions of the Fundus Oculi, Brit. J. Ophth. 40:167-172 (March) 1956.

113. Torrents, E.; Cervino, J. M.; Ravera, J. J.; Saralegui, J. P., and Mussio Fournier, J. C.: Modifications de l'électrorétinogramme dans les états hyperthyroidiens, Presse méd. 1:4 (Jan. 4) 1956.

114. Crick, R. P.: Ocular Sarcoidosis, Tr. Ophth. Soc. U. Kingdom 75:189-206, 1955.

115. James, D. G.: Discussion, Tr. Ophth. Soc. U. Kingdom 75:198-201, 1955.

116. Ainslie, D., and James, D. G.: Ocular Sarcoidosis, Brit. M. J. 1:954-957 (April 28) 1956.

117. Morax, P. V.: Les localisations neuro-oculaires de la réticulo-endothéliose de Besnier-Boeck-Schaumann, Ann. ocul. 189:73-91 (Jan.) 1956.

118. Cross, A. G.: Ocular Sarcoidosis, Tr. Ophth. Soc. U. Kingdom 75:181-187, 1955.

119. Constantine, F. H.: General Manifestations and Symptoms of Collagen Diseases, A. M. A. Arch. Ophth. 56:544-547 (Oct.) 1956.

120. Zimmerman, L. E.: Pathology of Diffuse Collagen Diseases: Current Concepts, A. M. A. Arch. Ophth. 56:548-556 (Oct.) 1956.

121. Maumenee, A. E.: Ocular Manifestations of Collagen Diseases, A. M. A. Arch. Ophth. 56:557-562 (Oct.) 1956.

122. Hollenhorst, R. W., and Henderson, J. W.: The Ocular Manifestations of the Diffuse Collagen Diseases, Am. J. M. Sc. 221:211-222 (Feb.) 1951.

123. Guyton, J. S.: Differential Diagnosis of Collagen Diseases, A. M. A. Arch. Ophth. 56:563-567 (Oct.) 1956.

124. Contardo, R.: Evolution of the Collagen Diseases, A. M. A. Arch. Ophth. 56:568-576 (Oct.) 1956.

125. Leopold, I. H.: The Therapy of Collagen Diseases, A. M. A. Arch. Ophth. 56:577-586 (Oct.) 1956.

126. Boeck, J.: Ocular Changes in Periarteritis Nodosa, Am. J. Ophth. 42:567-577 (Oct., Pt. 1) 1956.

127. Garcin, R.; Man, H. X., and Gruner, J.: Les Aspects ophtalmologiques de la périartérite noueuse, Presse méd. 2:1792-1794 (Dec. 25) 1955.

128. Kittel, V.: Augenbefunde bei Periarteritis nodosa, Klin. Monatsbl. Augenh. 129: 300-305, 1956.

129. Cury, D.; Breakey, A. S., and Payne, B. F.: Allergic Granulomatous Angiitis Associated with Uveoscleritis and Papilledema, A. M. A. Arch. Ophth. 55:261-266 (Feb.) 1956.

130. Müller, H.: Zur Klinik und Histologie der rezidivierenden Hypopyon-Uveitis mit Angiitis obliterans der Retina, Klin. Monatsbl. Augehn. 129:289-300, 1956.

131. Zetterström, R., and Berglund, G.: Systemic Lupus Erythematosus in Childhood: A Clinical Study, Acta pædiat. 45:189-204 (March) 1956.

132. Appelmans, M.; Michiels, J., and Missotten, L.: Cataracte et autres complications oculaires du syndrome sans pouls, Arch. opht. 16:5-11 (Jan.-Feb.) 1956; Bull. Soc. belge opht. 110:141-150 (June) 1955.

133. Pinkham, R. A.: The Ocular Manifestations of the Pulseless Syndrome, Acta XVII Conc. Ophth. (1954) 1:348-364, 1955.

134. Trias De Bes, L.; Lucas, J. G. S., and Barcons, F. B.: A Case of Takayashu's Syndrome: The Pulseless Disease, Brit. Heart J. 17:484-488 (Oct.) 1955.

135. Kimura, S. J.; Carriker, F. R., and Hogan, M. J.: Retinal Vasculitis with Intraocular Hemorrhage: Classification and Results of Special Studies, A. M. A. Arch. Ophth. 56: 361-374 (Sept.) 1956.

136. François, J., and De Rouck, A.: L'Électrorétinographie dans la periphlebite rétinienne, Acta ophth. 34:195-200, 1956.

137. Franceschetti, A., and Forni, S.: Surgical Treatment (Surface Diathermo-Coagulation) of Eales' Disease, Acta XVII Conc. Ophth. (1954) 1:215-222, 1955.

138. Kearns, T. P.: Changes in the Ocular Fundus in Blood Diseases, M. Clin. North America 40:1209-1216 (July) 1956.

139. Wasilewski, M.: Retinal and Preretinal Hemorrhages After Blood Transfusion, Post. okul. 1:177-184, 1954; abstracted, Am. J. Ophth. 41:732 (April) 1956.

140. Brihaye-van Geertruyden, M.: Retinal Lesions in Hodgkin's Disease, A. M. A. Arch. Ophth. 56:94-99 (July) 1956.

141. Cucco, G., and Pende, G.: Fundus Changes in Plasmocytoma, Ann. ottal. e clin. ocul. 81:477-493 (Nov.) 1955; abstracted, Am. J. Ophth. 42:341 (Aug.) 1956.

142. Bronstein, M.: Ocular Involvement in Multiple Myeloma, A. M. A. Arch. Ophth. 55: 188-192 (Feb.) 1956.

143. Danis, P.; Brauman, J., and Coppez, P.: Les Lésions du fond d'oeil au cours de certaines hyperproteinémies, en particulier celles d'origine myélomateuse, Acta XVII Conc. Ophth. (1954) 2:1042-1047, 1955.

144. Myerson, R. M., and Stout, R. E.: Cryoglobulinemia Associated with Gangrene of the Digits, Am. J. M. Sc. 230:499-505 (Nov.) 1955.

145. Ellis, R. A., and Klotz, J.: Cryoglobulinemia, abstracted, A. M. A. Arch. Ophth. 55:583-584 (April) 1956.

146. Keith, C. G.: Angioid Streaks and Pseudoxanthoma Elasticum, Brit. J. Ophth. 40:480-486 (Aug.) 1956.

147. Liegl, O.: Pseudoxanthoma elasticum mit Drusen am Augenhintergrund ohne Pigmentstreifen, Klin. Monatsbl. Augenh. 128:467-473, 1956.

148. Valenzuela Encina, R.: Estrias Angioides, Arch. chilen. oftal. 12:162-165 (Aug.-Dec.) 1955.

149. Bischler, V.: Le Fond d'oeil moucheté multicolore, manifestation fruste de la maladie de Groenblad et Strandberg, Bull. et mém. Soc. franç. opht. 68:287-291 (May) 1955.

150. Renard, G., and Brégeat, P.: Formes frustes et limites de l'angiomatose rétinienne, Bull. et mém. Soc. franç. opht. 68:239-247 (May) 1955.

151. Dollfus, M. A.: Discussion, Bull. et mém. Soc. franç. opht. 68:245 (May) 1955.

152. Doden, W., and Adams, A.: Ergebnisse neurologischer Untersuchungen von Kranken mit Periphlebitis retinae, Klin. Monatsbl. Augenh. 129:305-317, 1956.

153. Orbán, T.: Beiträge zu den Augenhintergrundsveränderungen bei Sclerosis multiplex, Ophthalmologica 130:387-396 (Dec.) 1955.

154. Schwab, F.: Die Augenhintergrundveränderungen bei tuberöser Hirnsklerose, Klin. Monatsbl. Augenh. 128:257-297, 1956.

155. Leipert, G.: Fetthaltiges Kammerwasser und vorübergehende Lipaemia retinalis bei einem Fall von Sheehan'sscher Krankheit, Klin. Monatsbl. Augenh. 127:558-565, 1955.

156. Reynon, M., and Masbernard, A.: Le Fond d'oeil dans la porphyrie aiguë, Ann. ocul. 189:319-328 (March) 1956.

157. Remky, H.: L'Adaptation de la circulation cérébrale aux efforts physiologiques: Sa démonstration expérimentale par l'intermédiaire de la circulation rétinienne, Ann. ocul. 188:849-858 (Sept.) 1955.

158. Bailliart, P.: L'Hypotension isolée de l'ártère rétinienne: Son importance dans l'étude de certains états cérèbraux, Presse méd. 2:1592-1593 (Nov. 19) 1955.

159. Paufique, L., and Moreau, P-G.: La Tension de l'ártère rétinienne dans l'hypotension artérielle cérébrale orthostatique isolée, Bull. et mém. Soc. franç. opht. 68:213-217 (May) 1955.

160. Puig Solanes, M.: El Aspecto anátomoclínico de la enfermedad de Vogt-Koyanagi estudio de 14 casos personales, Acta XVII Conc. Ophth. (1954) 3:1714-1721, 1955.

161. McLean, J. M.; Clark, G.; Schepens, C. L.; Shafer, D. M., and Shipman, J. S.: Symposium on Retinal Detachment, Am. J. Ophth. 41:698-711 (April) 1956.

162. Thiel, H-L.: Zur topographischen und histologischen Situation der Ora serrata, von Graefes Arch. Ophth. 156:590-629 (Oct.) 1955.

163. Samuels, S. L.: Cystoid Degeneration (Blessig-Iwanoff) of the Retina, Acta XVII Conc. Ophth. (1954) 1:114-116, 1955.

164. Fison, L.: Observations on Retinal Detachments, Tr. Ophth. Soc. U. Kingdom 75: 43-49, 1955.

165. Brockhurst, R. J.: Modern Indirect Ophthalmoscopy, Am. J. Ophth. 41:265-272 (Feb.) 1956.

166. Verhoeff, F. H.: Are Moore's Lightning Streaks of Serious Portent? Am. J. Ophth. 41: 837-840 (May) 1956.

167. Mundt, G. H., Jr., and Hughes, W. F., Jr.: Ultrasonics in Ocular Diagnosis, Am. J. Ophth. 41:488-498 (March) 1956.

168. Graupner, F.: Ein Beitrag zur Pathologie der Glaskörperblutungen, abstracted, Zentralbl. ges. Ophth. 65:323, 1955.

169. Marchessi, F.: A Case of Retinal Tear Discussion of the Pathogenesis of Retinal De- Without Detachment Followed for 2 Years: A tachment, Arch. Soc. oftal. hispano-am. 15: 662-681 (June) 1955; abstracted, Am. J. Ophth. 41:349 (Feb.) 1956.

170. Alajmo, A.: Histamine Content of Subretinal Fluid in Retinal Detachment, Gior. ital. oftal. 8:289-291 (July-Aug.) 1955; abstracted, Am. J. Ophth. 41:561 (March) 1956.

171. De Vincentiis, M.: Cholinesterase in the Subretinal Fluid, Arch. ottal. 59:434-447 (Sept.-Oct.) 1955; abstracted, Am. J. Ophth. 41:569 (March) 1956.

172. Dorello, U.: Electrophoretic Studies of the Protein Content of the Subretinal Fluid in Idiopathic Retinal Detachment, Arch. ottal. 59: 416-422 (Sept.-Oct.) 1955; abstracted, Am. J. Ophth. 41:564 (March) 1956.

173. Adams, S. T.: Retinal Breaks in Eye Bank Eyes, A. M. A. Arch. Ophth. 55:254-260 (Feb.) 1956.

174. Hagedoorn, A., and Sieger, D. H.: Idiopathic Retinal Detachment, Am. J. Ophth. 41:660-667 (April) 1956.

175. Michaelson, I. C.: Retinal Detachment: Clinical Evidence of the Role of the Choroid, Acta XVII Conc. Ophth. (1954) 1:392-400, 1955.

176. Prewitt, L. H.: Retinal Detachment Possibly Due to Stress, Parasympathotonia, and Non-Adaptation Syndromes: Report of a Case, Ann. Allergy 13:690-694 (Nov.-Dec.) 1955.

177. Lincoff, H. A.; Wise, G. N., and Romaine, H. H.: Total Detachment and Reattachment of the Retina: In Herpes Zoster Ophthalmicus, Am. J. Ophth. 41:253-256 (Feb.) 1956.

178. Ourgaud, A-G., and Bérard, P-V.: Décollement rétinien et hypertonie oculaire, Bull. et mém. Soc. franç. opht. 68:384-390 (May) 1955.

179. Nesserov, A.: Detachment of Retina in a Glaucomatous Eye, Vestnik oftal. 34:34 (May-June) 1956; abstracted, Am. J. Ophth. 41:1106 (June) 1956.

180. Jaeger, W.: Beitrag zur Ätiologie der Ora-Abrisse im temporalen unteren Quadranten, Klin. Monatsbl. Augenh. 127:423-427, 1955.

181. Frey, R. G.: Beiderseitige idiopathische Netzhautabhebung mit symmetrischen Desinsertionen bei Jugendlichen, Klin. Monatsbl. Augenh. 128:50-57, 1956.

182. Pau, H.: Die Entstehung der idiopathischen Netzhautablösung, Klin. Monatsbl. Augenh. 128: 568-573, 1956.

183. Abboud, I.: Retinal Detachment After D. F. P., Bull. Ophth. Soc. Egypt 58:167-168, 1955.

184. Weekers, R., and Lavergne, G.: Décollement de la rétine provoqué par le diisopropylfluorophosphonate (D. F. P.), Bull. Soc. belge opht. 110:273-276 (June) 1955.

185. Asbury, T., and Vaughan, D. G., Jr.: Experimental Scleral Surgery of the Monkey, Am. J. Ophth. 42:36-49 (July) 1956.

186. Everett, W. G.: An Experimental Evaluation of Scleral Shortening Operations, A. M. A. Arch. Ophth. 56:34-47 (July) 1956.

187. Everett, W. G.: Experimental Study of Modifications of the Scleral Fold Operation, Am. J. Ophth. 42:95-103 (Oct., Pt. 2) 1956.

188. Dellaporta, A.: Experimental Studies on a Scleral Buckling Operation, Am. J. Ophth. 42: 189-204 (Aug.) 1956.

189. Capper, S. A., and Leopold, I. H.: Mechanism of Serous Choroidal Detachment: A Review and Experimental Study, A M. A. Arch. Ophth. 55:101-113 (Jan.) 1956.

190. Linnen, H. J., and Hammers, H.: Beobachtungen bei künstlich erzeugter Amotio chorioideae, Klin. Monatsbl. Augenh. 129:319-324, 1956.

191. Dyster-Aas, K., and Krakau, C. E. T.: Experimental Eye Surgery with a Micromanipulator, Acta ophth. 34:300-310, 1956.

192. Knoll, H. A.: Ocular Impedance, Tissue Healing, and Scleral Shrinkage in Relation to Electrosurgical Treatment of Retinal Detachment, Am. J. Ophth. 41:542 (March) 1956.

193. Shipman, J. S., and Luce, C. M.: The Bilaterality of Retinal Separation, Acta XVII Conc. Ophth. (1954) 2:1050-1055, 1955.

194. Odic, R., and Nectoux, M. R.: Résultats opératoires éloignés du décollement de la rétine au point de vue social, Bull. et mém. Soc. franç. opht. 68:392-399 (May) 1955.

195. Funder, W.: Das Schicksal der einseitig an Netzhautabhebung Erblindeten, Klin. Monatsbl. Augenh. 129:330-335, 1956.

196. Funder, W.: Die Netzhautabhebung in aphaken Auge, von Graefes Arch. Ophth. 157:40-50; 51-61; 62-71, 1955.

197. Taubitz, W.: Bericht über 206 operierte Fälle von Netzhautablösung, Klin. Monatsbl. Augenh. 128:473-479, 1956.

198. Klomp, G.: Bericht über die Ergebnisse von 713 Netzhautoperationen unter besonderer Berücksichtigung der Netzhautablösungen ohne aufgefundenen Riss, Klin. Monatsbl. Augenh. 128:561-568, 1956.

199. vom Hofe, K.: Über Rezidive bei Netzhautablösungen, Klin. Monatsbl. Augenh. 128:557-561, 1956.

200. Asbury, T., and Vaughan, D. G., Jr.: Retinal Detachment Surgery, Am. J. Ophth. 41:247-253 (Feb.) 1956.

201. Vit, H.: Erfahrungen mit der Bulbusverkürzung durch lamellierende Skleralexzision bei Ablatio retinae, Klin. Monatsbl. Augenh. 129:324-330, 1956.

202. Shapland, C. D.: Diathermy or Scleral Resection, Tr. Ophth. Soc. U. Kingdom 75:405-418, 1955.

203. Hruby, K.: Prospects and Limitations of the Combined Operation for Retinal Detachment, Acta XVII Conc. Ophth. (1954) 1:412-418, 1955.

204. Nataf, R.; Besnainou, R.; Reynon, M., and Spaier: A Propos de la résection sclérale dans le décollement de la rétine, Bull. et mém. Soc. franç. opht. 68:350-369 (May) 1955.

205. Schiff-Wertheimer, S.; Gaillard, G., and Figueroa, R.: Étude statistique de 176 cas de décollement de la rétine opérés par résection sclérale, Arch. opht. 15:830-838 (Nov.-Dec.) 1955.

206. Colyear, B. H., Jr., and Pischel, D. K.: Clinical Tears in the Retina Without Detachment, Am. J. Ophth. 41:773-792 (May) 1956.

207. Arruga, H.: La Oportunidad y la selección de la operación del desprendimiento de la rétina, Arch. chilen. oftal. 12:121-127 (Aug.-Dec.) 1955.

208. Arruga, H.: Problemas tecnicos en las operaciónes de desprendimiento de la rétina el vaciamiento del liquido sub retiniano, Acta XVII Conc. Ophth. (1954) 1:44-47, 1955.

209. Marin-Amat, M.: État actuel du traitement du décollement de la rétine amélioration du pronostic, Bull. et mém. Soc. franç. opht. 68:276-285 (May) 1955.

210. Jayle, G-E.: La Sclérotomie en volet, technique et statistique opératoire, Bull. et mém. Soc. franç. opht. 68:342-349 (May) 1955.

211. Chamlin, M., and Rubner, K.: Lamellar Undermining: A Preliminary Report on a Technique of Scleral Buckling for Retinal Detachment, Am. J. Ophth. 41:633-638 (April) 1956.

212. Meyer-Schwickerath, G.: Light-Coagulation: A New Method for the Treatment and Prevention of Retinal Detachment, Acta XVII Conc. Ophth. (1954) 1:404-410, 1955.

213. Meyer-Schwickerath, G.: Lichtkoagulation: Eine Methode zur Behandlung und Verhütung der Netzhautablösung, von Graefes Arch. Ophth. 156:2-34 (Dec.) 1954.

214. Meyer-Schwickerath, G.: La Photocoagulation du fond d'oeil et de l'iris, Ann. ocul. 189:532-548 (June) 1956.

215. Colyear, B. H., Jr., and Pischel, D. K.: Causes of Failure in Retinal Detachment Surgery, A. M. A. Arch. Ophth. 56:274-281 (Aug.) 1956.

216. Swan, K. C.; Christensen, L., and Weisel, J. T.: Choroidal Detachment in the

Surgical Treatment of Retinal Separation, A. M. A. Arch. Ophth. 55:240-245 (Feb.) 1956.

217. Dellaporta, A.: Fundus Changes in Postoperative Hypotony, Am. J. Ophth. 40:781-785 (Dec.) 1955.

218. Maggi Zavalia, J., and Zurbriggen, M. B.: Perturbaciones de la sensibilidad de la cornea despues de la resección escleral laminar, Arch. oftal. Buenos Aires 31:59-63 (Feb.) 1956.

219. Badtke, G.: Über Schwierigkeiten bei der Erkennung intraokularer Malignome, nebst Bemerkungen zur Therapie und histologischen Auswertung der echten Melanozytoblastome, Klin. Monatsbl. Augenh. 128:526-544, 1956.

220. Bettman, J. W., and Fellows, V.: The Differential Diagnosis of Dark Lesions of the Posterior Fundus, Am. J. Ophth. 41:975-980 (June) 1956.

221. Dahlberg-Parrow, R.: Congenital Sex-linked Pseudoglioma and Grave Mental Deficiency, Acta ophth. 34:250-254, 1956.

222. Reese, A. B., and Jones, I. S.: Benign Melanomas of the Retinal Pigment Epithelium, Am. J. Ophth. 42:207-212 (Aug.) 1956.

223. Halldén, U.: Malignant Melanoma of the Chorioid Clinically Simulating Scleritis Attended by Amotio Retinae, Acta ophth. 33: 489-491, 1955.

224. Eoche-Duval, L.; Hervouet, F., and Lenoir, A.: Problème diagnostic posé par un méningiome intrachoroïdien, Bull. et mém. Soc. franç. opht. 68:324-330 (May) 1955.

225. Nover, A.: Über das Vorkommen multipler maligner Primärtumoren, von Graefes Arch. Ophth. 157:237-259, 1956.

226. McLean, J. M.: Glial Tumors of the Retina in Relation to Tuberous Sclerosis, Tr. Am. Ophth. Soc. 53:209-218, 1955; Am. J. Ophth. 41:428-432 (March) 1956.

227. Vogel, A. W., and Naib, K.: A Study of Intraocular Vx2 and Its Treatment, Am. J. Ophth. 42:27-44 (Oct., Pt. 2) 1956.

228. Terner, I. S.; Leopold, I. H., and Eisenberg, I. J.: The Radioactive Phosphorus (P^{32}) Uptake Test in Ophthalmology: A Review of the Literature and Analysis of Results in 262 Cases of Ocular and Adnexal Pathology, A. M. A. Arch. Ophth. 55:52-83 (Jan.) 1956.

229. Owens, W. C.; King, J. H., Jr., and Wells, H. S.: Radioactive Phosphorus for the Detection of Intraocular Tumors, Am. J. Ophth. 41:507-513 (March) 1956.

230. Palin, A., and Tudway, R. C.: The Use of Radioactive Isotopes in the Diagnosis of Intra-Ocular Malignancy, Tr. Ophth. Soc. U. Kingdom 75:281-299, 1955.

231. Herm, R. J., and Heath, P.: A Study of Retinoblastoma, Am. J. Ophth. 41:22-30 (Jan.) 1956.

232. Reese, A. B.; Hyman, G. A.; Merriam, G. R., Jr., and Forrest, A. W.: The Treatment of Retinoblastoma by Radiation and Triethylene Melamine (Tem), Acta XVII Conc. Ophth. (1954) 2:672-673, 1955.

233. Nonnenmacher, H.: Beitrag zum Glioma retinae, seiner Erblichkeit und Behandlung, Klin. Monatsbl. Augenh. 127:735-746, 1955.

234. Nover, A., and Oehlert, W.: Zur Genese des Retinoblastoms, Klin. Monatsbl. Augenh. 128:549-557, 1956.

235. Valière-Vialeix, C.; Cellier, and Robin, A.: Cas trés rare de gliome rétinien au sens histologique du mot, Bull. et mém. Soc. franç. opht. 68:263-272 (May) 1955.

236. Steward, J. K.; Smith, J. L. S., and Arnold, E. L.: Spontaneous Regression of Retinoblastoma, Brit. J. Ophth. 40:449-461 (Aug.) 1956.

237. Joyce, A., and Scott, R. K.: Treatment of Intra-Ocular Tumours with Radon, Acta XVII Conc. Ophth. (1954) 1:453-460, 1955.

238. Sébas, S. R.: Considerações sôbre o retinoblastoma, Rev. brasil. oftal. 15:63-68 (March) 1956.

239. Davies, W. S., and Thumim, M.: Cavernous Hemangioma of the Optic Disc and Retina, Tr. Am. Acad. Ophth. 60:217-218 (March-April) 1956.

240. Handl, O.: Zur Behandlung der Angiomatosis retinae, Klin. Monatsbl. Augenh. 128: 62-70, 1956.

241. Kronenberg, B.: Diathermic Surgery for a Case of Angiomatosis Retinae, A. M. A. Arch. Ophth. 55:25-27 (Jan.) 1956.

242. Charamis, J.: Sur le Traitement opératoire de l'angiomatose de la rétine, Bull. et mém. Soc. Franç. opht. 68:248-252 (May) 1955.

243. Kaufman, S. I., and Bennin, M.: Hemangioblastoma Retinae (von Hippel's Disease): Diathermy as the Treatment of Choice in Early Cases, Acta XVII Conc. Ophth. (1954) 3:1617-1622, 1955.

244. Weve, H. J. J.: Discussion, Acta XVII Conc. Ophth. (1954) 3:1625, 1955.

245. Hallermann, W.: Zur Diagnose und Behandlung des Aderhautangioms (Histologischer Befund einer elektrokoagulierten Tumors), Klin. Monatsbl. Augenh. 127:694-701, 1955.

246. Callahan, A.: Angiomatosis Retinae: Report of a Case with Histologic Examination, A. M. A. Arch. Ophth. 56:16-18 (July) 1956.

247. Reese, A. B.: Telangiectasis of the Retina and Coats' Disease, Am. J. Ophth. 42: 1-8 (July) 1956.

248. Falls, H. F.: Genetic Causes of Congenital Malformation of the Eyes, Acta XVII Conc. Ophth. (1954) 3:2060-2069, 1955.

249. Falls, H. F.: Genetic Prognostication and Counseling in Ophthalmology, Tr. Am. Acad. Ophth. 60:576-585 (July-Aug.) 1956.

250. Wolter, J. R.: Über besondere Astroglia an der Innenfläche der Retina, Klin. Monatsbl. Augenh. 129:224-230, 1956.

251. Fuchs, A.: Drusen of the Lamina Vitrea: A Discussion of Their Difference in Europe, the United States, and China, Am. J. Ophth. 41:840-846 (May) 1956.

252. Pillat, A.: The Aging of the Retina, Tr. Am. Acad. Ophth. 60:206-209 (March-April) 1956.

253. François, J.; Verriest, G., and de Rouck, A.: La Maladie d'Oguchi, Ophthalmologica 131:1-40 (Jan.) 1956.

254. François, J.; Verriest, G., and De Rouck, A.: Pathology of the X-Wave of the Human Electroretinogram: 1. Red-Blindness and Other Congenital Functional Abnormalities, Brit. J. Ophth. 40:439-443 (July) 1956.

255. Tansley, K.: Inherited Retinal Degenerations in Animals, Acta XVII Conc. Ophth. (1954) 3:1918-1924, 1955.

256. Chow, K. L.: Disuse and Retrograde Degeneration of Retinal Ganglion Cells, abstracted, Am. J. Ophth. 41:1068-1069 (June) 1956.

257. Lucas, D. R.: Retinitis Pigmentosa: Pathological Findings in 2 Cases, Brit. J. Ophth. 40:14-23 (Jan.) 1956.

258. Campbell, D. R., and Gebertt, S.: Cases of Retinitis Pigmentosa and Choroideremia Treated with Intermedin, Tr. Ophth. Soc. U. Kingdom 75:667-682, 1955.

259. Yung-Lin, H.: Unilateral Primary Pigmentary Degeneration of the Retina, Chinese M. J. 73:524-526 (Nov.-Dec.) 1955.

260. Turtz, C. A.: Unilateral Retinitis Pigmentosa, Am. J. Ophth. 41:308-310 (Feb.) 1956.

261. Knoll, A.: Simultaneous Occurrence of Pigment Degeneration of the Retina, and Keratoconus, Ezemészet 4:165-168, 1955; abstracted, Am. J. Ophth. 42:186 (July) 1956.

262. Alajmo, A.: Anatomo-Pathological Antagonism Between Pigmentary Degeneration of the Retina and Retinal Detachment, Gior. ital. oftal. 8:223-228 (May-June) 1955; abstracted, Am. J. Ophth. 41:585 (March) 1956.

263. Landau, J., and Feinmesser, M.: Audiometric and Vestibular Examinations in Retinitis Pigmentosa, Brit. J. Ophth. 40:40-44 (Jan.) 1956.

264. Wolter, J. R.: Rosetten der Netzhaut in einem Fall von fortgeschrittener Retinitis pigmentosa, Klin. Monatsbl. Augenh. 127:687-694, 1955.

265. François, J.; Verriest, G., and De Rouck, A.: Les Fonctions visuelles dans les dégénérescences tapéto-rétiniennes, Ophthalmologica, Supp. 43, pp. 1-86, 1956.

266. Zeavin, B. H., and Wald, G.: Rod and Cone Vision in Retinitis Pigmentosa, Am. J. Ophth. 42:253-268 (Oct., Pt. 2) 1956.

267. Iser, G., and Goodman, G.: Clinical Studies with Flicker Electroretinography, Am. J. Ophth. 42:227-237 (Oct., Pt. 2) 1956.

268. Dhanda, R. P.: Electroretinography in Night Blindness and Other Vitamin-A Deficiencies, A. M. A. Arch. Ophth. 54:841-849 (Dec.) 1955.

269. Sorsby, A., and Savory, M.: Choroidal Sclerosis: A Possible Intermediate Sex-Linked Form, Brit. J. Ophth. 40:90-95 (Feb.) 1956.

270. Westerlund, E.: Inheritance of Choroideremia, Acta ophth. 34:63-68, 1956.

271. Horwich, H., and Linfesty, J. W.: Pseudostrabismus Caused by Heterotopia of the Macula: Report of a Case and Review of the Literature, A. M. A. Arch. Ophth. 56:194-206 (Aug.) 1956.

272. Payne, I. W., and Crick, R. P.: Ectopia of the Macula, Brit. J. Ophth. 40:492-496 (Aug.) 1956.

273. Tower, P.: Observations on Hole in the Macula, Ophthalmologica, Supp. 40, pp. 3-60, 1954.

274. de Vincentiis, M.: The Pathogenesis of the Macular Hole, Arch. ottal. 59:345-352 (July-Aug.) 1955; abstracted, Am. J. Ophth. 41:350 (Feb.) 1956.

275. Sorsby, A.; Savory, M.; Davey, J. B., and Fraser, R. J. L.: Macular Cysts: A Dominantly Inherited Affection with a Progressive Course, Brit. J. Ophth. 40:144-158 (March) 1956.

276. Steinmetz, R. D.; Ogle, K. N., and Rucker, C. W.: Some Physiologic Considerations of Hereditary Macular Degeneration, Am. J. Ophth. 42:304-317 (Oct. Pt. 2) 1956.

277. Hertzberg, R.: Tay-Sachs Disease: Report of Three Cases in One Family, M. J. Australia 1:664-665 (April 21) 1956.

278. Hoffman, J.: Pigmentary Retinal Lipoid Neuronal Heredodegeneration (Spielmeyer-Vogt Disease), Am. J. Ophth. 42:15-21 (July) 1956.

279. Goslich, H.: Klinische und elektroretinographische Untersuchungen in 3 Genera-

tionen von familiär-hereditärer juveniler Makula-degeneration (Stargardt), Klin. Monatsbl. Augenh. 127:657-663, 1955.

280. Jacobson, J. H.; Basar, D., and Kornzweig, A. L.: Spectrodifferential Electroretinography in Macular Disease, Am. J. Ophth. 42: 199-205 (Oct., Pt. 2) 1956.

281. Wadensten, L.: The Use of Flicker Electroretinography in the Human Eye, Acta ophth. 34:311-340, 1956.

282. Mitsui, Y., and Sakanashi, R.: Central Angiospastic Retinopathy, Am. J. Ophth. 41: 105-114 (Jan.) 1956.

283. Wolkowicz, M. I.: Central Serous Retinopathy: Clinical and Experimental Studies, Am. J. Ophth. 42:531-545 (Oct., Pt. 1) 1956.

284. Seitz, R.: Beitrag zur Chorioretinitis centralis serosa, Klin. Monatsbl. Augenh. 127: 676-687, 1955.

285. Rusodimos, C. N.: Central Angiospastic Retinopathy, Arch. Soc. oftal. hispano-am. 15: 530-538 (May) 1955; abstracted, Am. J. Ophth. 41:350 (Feb.) 1956.

286. Gordon, D. M.: Prednisone and Prednisolone in Ocular Disease, Am. J. Ophth. 41: 593-600 (April) 1956.

287. Nicholls, J. V. V.: Concurrence of Macular Edema with Cataract Extraction, A. M. A. Arch. Ophth. 55:595-604 (May) 1956.

288. Bedell, A. J.: The Importance of Ophthalmoscopic Photographs in Forensic Medicine: Kodachromes, Tr. Am. Ophth. Soc. 53: 63-73, 1955.

289. Norton, H. J., Jr.: Absolute Electronic Retinal Stereophotography, Am. J. Ophth. 40: 809-817 (Dec.) 1955.

290. Goodside, V.: The Anterior Limiting Membrane and the Retinal Light Reflexes, Am. J. Ophth. 41:288-292 (Feb.) 1956.

291. Gregg, N.: Congenital Anomalies Due to Maternal Infections Especially in the Early Months of Pregnancy, Tr. Am. Acad. Ophth. 60:199-205 (March-April) 1956.

292. Siegert, P.: Über Augenerkrankungen bei mangelernährten Spätheimkehrern, Klin. Monatsbl. Augenh. 129:3-13, 1956.

293. Noell, W. K., and Cibis, P. A.: Experimental Pathology of Retinal Degeneration, Acta XVII Conc. Ophth. (1954) 3:1954-1957, 1955.

294. Rugh, R., and Wolff, J.: Reparation of the Fetal Eye Following X-Irradiation, abstracted, Am. J. Ophth. 42:134-135 (July) 1956.

295. Brown, D. V. L.; Cibis, P. A., and Pickering, J. E.: Ocular Effects Following Head, Body, or Whole Body Exposure to Co^{60} Gamma Rays, Am. J. Ophth. 42:309 (Aug.) 1956.

296. Newell, F. W.; Harper, P. V., Jr., and Köistenen, A.: Irradiation of the Posterior Ocular Segment with Radioactive Yttrium, Am. J. Ophth. 42:85-88 (July) 1956.

297. Burmeister, H.: Erfahrungen bei der Bestrahlung des Auges mit Mikrowellen, Klin. Monatsbl. Augenh. 129:336-342, 1956.

298. Jonquères, J., and de Saint-Martin, P-L.: Les Manifestations choriorétiniennes des électrocutions, Arch. opht. 16:397-403 (June) 1956.

299. Byrnes, V. A.; Brown, D. V. L.; Rose, H. W., and Cibis, P. A.: Chorioretinal Lesions Due to Thermal Radiation from the Atomic Bomb, A. M. A. Arch. Ophth. 55:909-914 (June) 1956.

300. Rose, H. W.; Brown, D. V. L.; Byrnes, V. A., and Cibis, P. A.: Human Chorioretinal Burns from Atomic Fireballs, A. M. A. Arch. Ophth. 55:205-210 (Feb.) 1956.

301. Chambers, A. L.: The Use of Cortisone in Treatment of Chorio-Retinal Damage Resulting from Observation of Atomic Detonation, Military Med. 117:338-342 (Oct.) 1955.

302. Das, T.; Nirankari, M. S., and Chaddah, M. R.: Solar Chorioretinal Burn, Am. J. Ophth. 41:1048-1053 (June) 1956.

303. Meyerratken, E.: Über Makulaschädigung durch Beobachtung der Sonnenfinsternis vom 30. Juni 1954, Klin. Monatsbl. Augenh. 129:78-87, 1956.

304. Gebertt, S.: Immediate Results of Treating Sun-Blindness with Carbachol Injections, Brit. M. J. 1:95 (Jan. 14) 1956.

305. Münchow, W.: Einfache Methode zur Überprüfung von Makulaschäden, Klin. Monatsbl. Augenh. 129:94-96, 1956.

306. Meyer-Schwickerath, G.; Grüterich, E., and Niesel, P.: Die Wirkung von Butazolidin auf experimentelle Entzündungen am Augenhintergrund, Klin. Monatsbl. Augenh. 129:358-365, 1956.

307. Dische, Z.: Physiological Chemistry of the Eye: A Review of Papers Published During 1955, A. M. A. Arch. Ophth. 56:587-634 (Oct.) 1956.

308. Apter, J. T., and Pfeiffer, C. C.: Effect of Hallucinogenic Drugs on the Electroretinogram, Am. J. Ophth. 42:206-210 (Oct., Pt. 2) 1956.

309. Leplat, G., and Gerebtzoff, M. A.: Localisation de l'acétylcholinestérase et des mediateurs diphénoliques dans la rétine, Ann. ocul. 189:121-128 (Jan.) 1956.

310. Kornblueth, W., and Ben-Shlomo, E.: Glucose Utilization of the Retina: IV. Influence of Toxic Substances and Enzyme Inhibitors, A. M. A. Arch. Ophth. 55:813-817 (June) 1956.

311. Nishi, T.: Diseases of the Eye Caused by Sensitization and Provocative Injection with Egg White in Rabbits: Injection into Anterior Chamber, Vitreous Body and Retrobulbar Space, Acta Soc. ophth. japon. 59:1666-1675 (Oct.) 1955; abstracted, Am. J. Ophth. 41:560 (March) 1956.

312. Carroll, F. D.; Henderson, J. W.; Zimmerman, L. E.; Walsh, F. B., and Rucker, C. W.: Symposium: Diseases of the Optic Nerve, Tr. Am. Acad. Ophth. 60:7-98 (Jan.-Feb.) 1956.

313. Dubois-Poulsen, A.: Reproduction expérimentale du ressaut de Rönne et du scotome de Bjerrum, Ann. ocul. 189:37-52 (Jan.) 1956.

314. Trantas, N. G.: La Recherche de la photosensibilité de la rétine par un simple moyen ophtalmoscopique, Acta XVII Conc. Ophth. (1954) 3:1748-1755, 1955.

315. François, J., and Neetens, A.: Vascularization of the Optic Pathway: III. Study of Intra-Orbital and Intracranial Optic Nerve by Serial Sections, Brit. J. Ophth. 40:45-52 (Jan.) 1956.

316. Wolter, J. R.: Reactions of the Elements of Retina and Optic Nerve: In Common Morbid Entities of the Human Eye, Am. J. Ophth. 42:10-26 (Oct., Pt. 2) 1956.

317. Niedermeier, S.: Experimentelle Untersuchungen zur Pathogenese der Stauungspapille, von Graefes Arch. Ophth. 157:397-406, 1956.

318. Minton, J.: Intracranial Aneurysms of the Internal Carotid and Cerebral Arteries, Tr. Ophth. Soc. U. Kingdom 75:81-100, 1955.

319. Wagener, H. P.: Lesions of the Optic Nerve in Exophthalmos of Endocrine Origin, Am. J. M. Sc. 232:226-239 (Aug.) 1956.

320. Hedges, T. R., Jr., and Scheie, H. G.: Visual Field Defects in Exophthalmos Associated with Thyroid Disease, A. M. A. Arch. Ophth. 54:885-892 (Dec.) 1955.

321. Rizzoli, E.: A Case of Duplication of the Papilla, Rass. ital. ottal. 24:352-362 (Sept.-Oct.) 1955; abstracted, Am. J. Ophth. 41:1123 (June) 1956.

322. Vauthier, D., and Zanen, J.: Fossettes papillaires, Bull. Soc. belge opht. 110:162-169 (June) 1955.

323. Sena, J. A.; Cerboni, F. C., and Kutyn, J.: Excrecenciás hialinas de la papila, Arch. oftal. Buenos Aires 30:447-452 (Nov.) 1955.

324. la Rocca, V.: Atypical Coloboma of the Choroid and of the Optic Disk, Gior. ital. oftal. 8:348-351 (July-Aug.) 1955; abstracted, Am. J. Ophth. 41:741 (April) 1956.

325. Marquart, G.: Pseudostauungspapille, Klin. Monatsbl. Augenh. 127:546-558, 1955.

326. Kirichenko, E.: Evulsion of the Optic Disk, Vestnik oftal. 34:43 (March-April) 1955; abstracted, Am. J. Ophth. 41:1108 (June) 1956.

327. Landolt, E.: Zur Opticusschädigung bei Schädeltrauma, Acta neurochir. 4:128-142 (Feb.) 1955.

328. Martelli, A., and Strazzi, A.: Results of Early Surgical Intervention in Amauroses Secondary to Cranial Trauma, Riv. oto-neuro-oftal. 31:9-22 (Jan.-Feb.) 1956; abstracted, Am. J. Ophth. 42:340 (Aug.) 1956.

329. Kurachi, Y., and Yonemura, D.: Critical Fusion Frequency in Retrobulbar Neuritis, A. M. A. Arch. Ophth. 55:371-379 (March) 1956.

330. Steinmetz, R. D., and Kearns, T. P.: H-R-R Pseudo-Isochromatic Plates: As a Diagnostic Aid in Retrobulbar Neuritis of Multiple Sclerosis, Am. J. Ophth. 41:833-837 (May) 1956.

331. Victoria, V.: Leber's Disease: Report of an Affected Family, Arch. oftal. Buenos Aires 30:249-256 (July) 1955; abstracted, Am. J. Ophth. 41:367-368 (Feb.) 1956.

332. Ros Pena, R.: Leber's Hereditary Optic Atrophy, Arch. Soc. oftal. hispano-am. 15:1262-1270 (Nov.) 1955; abstracted, Am. J. Ophth. 41:1124 (June) 1956.

333. Velásquez, O.: Hereditary Optic Atrophy: Report of Ten Cases in Three Generations in One Family, Acta XVII Conc. Ophth. (1954) 3:1661-1666, 1955.

334. Glick, L., and Mumford, J.: Quinine Amblyopia: Treatment by Stellate Ganglion Block, Brit. M. J. 2:94-96 (July 9) 1955.

335. Gilger, A. P.; Potts, A. M., and Farkas, I. S.: Studies on the Visual Toxicity of Methanol: IX. The Effect of Ethanol on Methanol Poisoning in the Rhesus Monkey, Am. J. Ophth. 42:244-252 (Oct., Pt. 2) 1956.

336. Fornaro, L.: Gastric Function and Blood Crasis in Alcohol-Tobacco Amblyopia, Riv. oto-neuro-oftal. 31:44-59 (Jan.-Feb.) 1956; abstracted, Am. J. Ophth. 42:341 (Aug.) 1956.

337. Guttmann-Friedmann, A.: Blindness After Snake-Bite, Brit. J. Ophth. 40:57-59 (Jan.) 1956.

338. Marin Amat, M.: Ocular Manifestations in 100 Cases of Tuberculous Meningitis, Arch. Soc. oftal. hispano-am. 15:1193-1218 (Nov.) 1955; abstracted, Am. J. Ophth. 41:1120 (June) 1956.

339. Mooney, A. J.: Some Ocular Sequelae of Tuberculous Meningitis: A Preliminary Survey, 1953-1954, Am. J. Ophth. 41:753-768 (May) 1956.

340. Stagni, S.: Treatment of Chronic Retrobulbar Neuritis with Retrobulbar Injections

of Nicotinic Acid, Gior. ital. oftal. 8:335-347 (July-Aug.) 1955; abstracted, Am. J. Ophth. 41:589 (March) 1956.

341. Brihaye-van Geertruyden, M.: Traitement d'une névrite rétrobulbaire unilatérale aiguë par injections rétrobulbaires répétées d'hydrocortisone, Arch. opht. 16:274-282 (April-May) 1956.

342. Wagener, H. P., and Horton, B. T.: Long-Continued Intravenous Administration of Histamine in Cases of Lesions of the Optic Nerve, Retina and Choroid: Report of an 11-Year Study, Acta XVII Conc. Ophth. (1954) 1:564-570, 1955.

343. Ferreira, L. E.: Atrofias do nervo optico, Rev. brasil. oftal. 15:69-93 (March) 1956.

344. Le Grand and Verlaeken: Les Troubles visuels posthémorragiques, Bull. Soc. belge opht. 110:126-137 (June) 1955.

345. Takahashi, M.: Anoxia in the Central Nervous System, Particularly in the Visual Pathway, Caused by Pitressin, Acta Soc. ophth. japon. 59:1388-1397 (Sept.) 1955; abstracted, Am. J. Ophth. 41:740 (April) 1956.

346. Klauder, J. V.: An Appreciation of Wassermann in Relation to Ocular Syphilis, A. M. A. Arch. Dermat. 73:464-468 (May) 1956.

347. Cutler, W. M., and Blatt, I. M.: The Ocular Manifestations of Lethal Midline Granuloma (Wegener's Granulomatosis), Am. J. Ophth. 42:21-35 (July) 1956.

348. Gross, H.: Zur Pathogenese der Sehnervenatrophie bei den turricephalen Schädeldysostosen, von Graefes Arch. Ophth. 157:225-236, 1956.

349. Hobbs, H. E.: Fibrous Dysplasia of the Bony Orbit, Acta XVII Conc. Ophth. (1954) 3:1756-1763, 1955.

350. Rychener, R. O., and Murphey, F.: Periorbital Fibrous Dysplasia, Tr. Am. Ophth. Soc. 53: 155-174, 1955.

351. Matteucci, P., and Kluzer, G.: Symptoms of Intracranial Compression of the Optic Nerve, Rass. ital. ottal. 24:325-337 (Sept.-Oct.) 1955; abstracted, Am. J. Ophth. 41:1108 (June) 1956.

352. Wolter, J. R., and Liss, L.: Histopathologie des Sehnerven bei direkter Kompression durch Tumor, Klin. Monatsbl. Augenh. 128:297-306, 1956.

353. Frezzotti, R.: Sul Valore localizzatore della sindrome di Foster Kennedy, Boll. ocul. 34:498-509 (Aug.) 1955.

354. Walsh, F. B.: The Ocular Signs of Tumors Involving the Anterior Visual Pathways: The Tenth Francis I. Proctor Lecture, Am. J. Ophth. 42:347-377 (Sept.) 1956.

355. Taveras, J. M.; Mount, L. A., and Wood, E. H.: The Value of Radiation Therapy in the Management of Glioma of the Optic Nerves and Chiasm, Radiology 66:518-528 (April) 1956.

356. Hanbery, J. W.: Gliomas of the Optic Nerve, Stanford M. Bull. 14:34-50 (Feb.) 1956.

357. Razumikhina, N.: Meningioma of the Optic Nerve, Vestnik oftal. 34:27-30 (March-April) 1955; abstracted, Am. J. Ophth. 41:1108-1109 (June) 1956.

Correspondence

STEREOPSIS AND UNEQUAL LUMINOSITIES OF THE IMAGES IN THE TWO EYES

To the Editor:—In the December, 1956, issue of the ARCHIVES, page 878, is published a paper entitled "Stereopsis and Unequal Luminosities of the Images in the Two Eyes," written by K. N. Ogle, Ph.D., and Judith Groch, B.S. This paper deals chiefly with a phenomenon I described in the ARCHIVES 23 years ago. Since these authors discredit the observations I reported, I feel called upon to comment upon their paper.

The phenomenon in question was the observation that when the luminosity of one disparate retinal image of an object was greatly reduced below that of the other image the depth effect was reduced and the apparent position of the object was shifted laterally. Ogle and Groch admit, although apparently with reluctance, the lateral shift of the object, but they deny the depth effect. They make this serious misstatement: "this lateral deviation, which Verhoeff stated is proportional to the difference in the luminosities, . . ." As a matter of fact, I was careful not to make such a statement in respect to either lateral deviation or depth. For, with the same difference in luminosity, the effects I have described could be marked when there was a relatively low intensity of illumination and not perceptible with a much higher intensity. To make the phenomenon recognizable the difference in luminosity must be great enough to make the luminosity of the weaker image very low. This fact is obvious from the specifications given in my paper, but I find that I did not emphasize it.

Ogle and Groch maintain that from their experiments "one would have to conclude that decreasing the luminosity of the image of one eye does not alter the physiologic disparity between the images of the two eyes or the stereoscopic depth. This conclusion is, of course, only true for static spatial line configurations. One must ask, then: What is the explanation of the observations made by Verhoeff and corroborated as well by other subjects? It is possible that the lateral inclination of the line toward the brighter image may have interfered with the stereoscopic depth. It is also possible, since this effect was found only with relatively dense filters, that the differential contrast threshold of the eye seeing the darkened target became too high for the line to be readily visible." These statements seem to mean that Ogle and Groch admit that the phenomenon may actually occur, although they have not been able to produce it. But they go on to say, "However, the answer most probably lies in the fact that, as so often is the case, the results of introspective observation can be misleading, for, when one attempts to measure the observed phenomena, they often are not found." I take this to mean that, at least as regards depth effect, the authors believe the phenomenon to be entirely imaginary.

Although my experiments were made about 24 years ago, I clearly remember them and am sure the results were not imaginary. The instrument, screens, etc., are no longer available to me, and therefore I cannot exactly reproduce these experiments. Nor can I attempt to reproduce the experiments made by Ogle and Groch. However, I find that for angular disparateness I can easily demonstrate the phenomenon by the use of an ordinary Brewster stereoscope, and for parallel disparateness, by the use of my "Stereopter." For a screen I use two pieces of polaroid film applied together. By suitably adjusting these pieces the required density is easily obtained. For the angular disparateness I employ two rotary discs of white cardboard, each 6.1 cm. in diameter and connected by cogs so that the discs rotate equally but in opposite directions. Centered on each disc is a vertical black line 4.6 cm. in length and 0.75 mm. in width and a circle 15 mm. in diameter. The circles provide an additional plane of reference. (The impor-

tance of such a plane of reference for the observation of stereoscopic phenomena is often overlooked.) After being placed in the stereoscope, the discs are rotated until the single line seen has a well-marked fore and aft slant. Then the polaroid screen is placed before one eye so as to obscure the lower or upper half of the disc seen by that eye. The density of the screen should be as great as possible and still permit screened half of the line to be definitely visible to the screened eye. Each observer can determine, by trials, the conditions suitable for him. Under these suitable conditions, when the screen is interposed the screened half of the line appears to swing so that it is at an angle with the other half. The displacement is both lateral and fore and aft, as I have described. When the screen is removed, the line appears to swing back to its original position.

The phenomenon is more pronounced for the lateral effect when two screens are used, one screen before the upper half of one disc, the other screen before the lower half of the other disc. The depth effect, however, can then be perceived only by comparing the slant of the line as seen with and without the screens. I have been able to produce the phenomenon without the use of a stereoscope, by viewing a single line slanted fore and aft from the vertical and screening for one eye one-half of it by the polaroid screen. The line can be black on white, or white on a black background.

In the case of vertical parallel lines, under some conditions, monocular criteria and preconceived ideas may prevent perception of the phenomenon. By the use of my "Stereopter" the deleterious effect upon the phenomenon of relative size can be abolished, and the phenomenon then is usually so apparent that preconceived ideas are overcome. The "Stereopter" is viewed at a distance of about 25 cm., and a set of strips is selected in which the widest strip is back and the narrowest strip forward and on the left. Bifixation is maintained on one of these strips. When the screen is placed before the right eye so as to obscure its whole field, the depth and also the lateral distance between the two strips appear to decrease. The same is true when the screen is placed before the left eye, if the "Stereopter" is turned upside down so that the forward strip is on the right. When the screen is removed, the strips seem to return to their original positions. Occasionally, for some obscure reason, while the screen is still in place, the apparent depth appears to become as great as it was without the screen. If, when this occurs, the screen is removed, no increase in depth may be observed. It would seem that the evidence supplied by an image with low luminosity may be so weak that it is sometimes rejected by consciousness, especially when there is competing evidence.

If Ogle and Groch will make the simple experiments I have just described, I am sure that they will become convinced that the phenomenon is not imaginary. They can then try to ascertain why their own experiments did not reveal it. Although they had admitted the lateral effect, they did not mention it in their summary. To me this effect is of greater scientific interest than the depth effect.

Presumably, this phenomenon is in itself of no practical importance because the conditions needed to produce it are not ordinarily encountered. However, it does bring up and perhaps help to answer some questions of fundamental importance. These relate to the apparent position of an object when its disparate images are seen as one and when they are seen as two and to the role of the subconscious in stereoscopic vision. From Ogle's writings I judge that he and his co-author still hold to the prevailing view that Panum's areas actually exist and therefore that "fusion" of disparate images can take place in the same sense as "fusion" of corresponding images. For many years I also believed this, but for about the past 25 years I have not. The experiments that I made 24 years ago, to which Ogle and Groch now call attention, played a part in the development of my theory of replacement, which rejects Panum's conception. In the light of this theory, published in the ARCHIVES in 1933, I discussed to some extent the questions to which I now refer, but I hope to discuss them more fully in the near future.

F. H. VERHOEFF, M.D.
403 Commonwealth Ave., Boston

News and Comment

ANNUAL MEETING OF AMERICAN MEDICAL ASSOCIATION

New York, June 3-7, 1957

Combined Meeting of Section on Ophthalmology with Association for Research in Ophthalmology

SECTION ON OPHTHALMOLOGY

Wednesday, June 5, 1957

Chairman's Address: The Differential Diagnosis of Melanoma of the Uvea from Simulating Lesions

A. B. REESE, New York

Address of Invited Foreign Guest: The Differential Diagnosis of the Tapeto-retinal Degenerations

PROF. J. FRANCOIS, Ghent, Belgium

Ocular Involvement in Nevoxanthoendothelioma: Report of Two Cases

FRANK W. NEWELL, Chicago
Discussion to be opened by T. E. SANDERS, St. Louis

Pars Plana Cysts

SAMUEL T. ADAMS, Montreal, Canada
Discussion to be opened by HERBERT M. KATZIN, New York

Improvement in the Hypertensive Retinopathy of One Hundred Nine Patients Following Combined Adrenal Resection and Sympathectomy

WILLIAM C. FRAYER, Philadelphia
Discussion to be opened by JOHN WENDLAND, Minneapolis

Malignant Melanoma of Uvea: Observations on Growth and Behavior, Enucleation Refused or Long Delayed

BANKS ANDERSON, Durham, N. C.
Discussion to be opened by LORENZ ZIMMERMAN, Washington, D. C.

Studies on Continuous Electrocardiography During Ocular Surgery

RALPH E. KIRSCH, Miami, Fla.
PHILIP SAMET, Miami, Fla.
VICTOR KUGEL, Miami, Fla.
Discussion to be opened by HAROLD F. FALLS, Ann Arbor, Mich.

Thursday, June 6, 1957

Executive Session

Address of Invited Foreign Guest: Iridencleisis in Buphthalmos

FRANK W. LAW, London, England

Evaluation of New Anticholinesterase Agents in Glaucoma

IRVING H. LEOPOLD, Philadelphia
DAVID GOLD, Philadelphia
PAUL GOLD, Philadelphia
Discussion to be opened by H. SAUL SUGAR, Detroit

A Surgical Approach to Total Xerophthalmia Through Transplantation of the Parotid Duct

JAMES E. BENNETT, Cleveland
ARBY L. BAILEY, Cleveland
Discussion to be opened by TRYGVE GUNDERSEN, Boston

New Aspects of Ophthalmoneurologic Diagnosis

GOODWIN M. BREININ, New York
Discussion to be opened by FRANCIS HEED ADLER, Philadelphia

Friday, June 7, 1957

Symposium on Problems in Cataract Extraction

Five Years Experience with the Ridley Operation

WARREN REESE, Philadelphia
TURGUT HAMDI, Philadelphia

Acrylic Lenses in the Anterior Chamber: Experimental Studies in Animals

J. H. KING JR., Washington, D. C.
RAYMOND SKEEHAN, Washington, D. C.

Clinical Report on Three Cases of Postoperative Epithelial Downgrowth Treated by Curettage and Cautery with Seventy Per Cent Alcohol

JOHN C. LONG, Denver
GEORGE S. TYNER, Denver

Cataract Extraction and Aqueous Outflow

JAMES E. MILLER, St. Louis
G. RICHARD KESKEY, St. Louis
BERNARD BECKER, St. Louis

Tonographic and Gonioscopic Studies Before and After Cataract Extraction

PEI-FEI LEE, Boston
ROBERT R. TROTTER, Boston

Contact Lenses in Aphakia

EVERETT L. GOAR, Houston, Texas

Comparison of the Peripheral Iridectomy vs. the Keyhole Iridectomy

DAVID S. JOHNSON, Detroit
RALPH PINO, Detroit

Conservatism in the Treatment of Congenital Cataract

FRANK D. COSTENBADER, Washington, D. C.
Discussion to be opened by JOHN DUNNINGTON, New York
PETER KRONFELD, Chicago
JOHN MCLEAN, New York
A. EDWARD MAUMENEE, Baltimore
DERRICK VAIL, Chicago

THE ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY

Tropical Room, Park Sheraton Hotel

Monday, June 3, 1957

9:00 Effects of Tachistoscopic Training on Visual Functions in Myopic Patients
CONRAD BERENS, LOUIS J. GIRARD, GERALD FONDA, and SAUL B. SELLS

9:20 The Human Optic Papilla: A Demonstration of New Anatomical and Pathological Findings
J. REIMER WOLTER

9:40 Continuing Studies on the Association of Adenovirus Type 8 with Epidemic Keratoconjunctivitis
L. HANNA, E. JAWETZ, Y. MITSUI, P. THYGESON, S. KIMURA, and A. NICHOLAS

10:00 Precipitating Antibodies to Toxoplasma: A Follow-Up Study of Findings in the Blood and Aqueous Humor
G. RICHARD O'CONNOR

10:20 Intermission

10:40 Factors Underlying the Development of the Ciliary Processes
ALFRED J. COULOMBRE and JANE L. COULOMBRE

11:00—The Effects of Maternal Hypoxia on Inheritance of Recessive Blindness in Mice
AELETA NICHOLS BARBER

11:20 Distribution of Radioactive Sulfate in the Developing Eye
GEORGE K. SMELSER and VICTORIA OZANICS

11:40 Oxygen Studies in Retrolental Fibroplasia: VI. The Effects of Concentration and Duration of Exposure to Oxygen on Experimental Ocular Lesions
ARNALL PATZ

1:30 The Response Pathway from Photoreceptor to Nerve Cells in the Limulus Lateral Eye
LEO E. LIPETZ

2:00 Studies of Photoreceptor Structures
JEROME J. WOLKEN

2:20 Electromyography of Fusional Movements
FREDERICK C. BLODI and MAURICE VAN ALLEN

2:40 Autonomic Innervation of Extraocular Eye Muscles
WALTER MITCHELL and GERHARD A. BRECHER

3:00 The Effect of Ultrasonic Radiation upon the Rate of Absorption of Blood from the Vitreous
GILBERT BAUM

3:20 Intermission

3:40 Ocular Effects of Systemic Siderosis
PAUL A. CIBIS, E. BROWN, and S. M. HONG

4:00 **Cytochemical and Morphological Changes in Corneal Stromal Cells Following Wounding**
VIRGINIA L. WEIMAR

4:20 **Further Studies on the Viability of Frozen Corneas: As Determined in Tissue Culture**
JERRY W. DRAHEIM, SAMUEL D. MCPHERSON JR., VIRGINIA J. EVANS, and WILTON R. EARLE

4:40 **Studies of Bruch's Membrane: I. Results of Flow Studies Through a Bruch's Membrane-Choroid Preparation**
WOOD LYDA, NILS ERIKSEN, and NARENDRA KRISHNA

Tuesday, June 4, 1957

1:30 **A Study of the Uptake of P^{32}, Zn^{65}, and I^{131} by Experimental Malignant Melanoma**
JAMES F. O'ROURKE, HUMPHREY PATTON, and ROBERT BRADLEY

2:00 **Anterior Chamber Perfusion Studies: II. Controlled Particle Size in Relationship to Pore Size**
PHILIP A. PETER, WOOD LYDA, and NARENDRA KRISHNA

2:20 **A Study of the Innervation of the Chamber Angle: II. The Origin of Trabecular Axons Revealed by Degeneration Studies**
MONTE G. HOLLAND, LUDWIG VON SALLMANN, and ELEANOR M. COLLINS

2:40 **The Effect of Succinylcholine on the Extraocular Striate Muscles and on the Intraocular Pressure**
F. J. MACRI

3:00 **On the Occurrence of Proteolytic Enzymes in Normal and Cataractous Lenses**
E. ALBERT ZELLER and ANIMA DEVI

3:20 **The Transcorneal Potential**
ALBERT M. POTTS and ROBERT MODRELL

3:40 **Intermission**

4:00 **Incorporation of S^{35}-Inorganic Sulfate into Mucopolysaccharides of Cornea**
BERNARD WORTMAN and JACK L. STROMINGER

4:20 **Friedenwald Memorial Lecture**

Wednesday, June 5, 1957

1:30 **In Vivo Intralenticular Implantation of Various Dyes and Enzyme Inhibitors**
ADOLPH W. VOGEL

2:00 **In Vitro Lens Studies: II. Production of Cataractous Changes**
MARGUERITE A. CONSTANT

2:20 **Studies on the Crystalline Lens: VIII. Ascorbic Acid and Mitotic Activity in Cultured Lenses**
V. EVERETT KINSEY

2:40 **Studies on the Sulfhydryl Groups of Lens**
LORENZO O. MEROLA and JIN H. KINOSHITA

3:00 **Business Meeting**

3:20 **Intermission**

3:40 **Studies on Protein and Protein Synthesis of the Lens in Galactose Cataract**
ZACHARIAS DISCHE, JOSHUA YOULUS, and GINEVRA ZELMENIS

4:00 **Insulin and the Lens**
T. FARKAS and JOHN W. PATTERSON

4:20 **Lens Proteins**
JULES FRANCOIS

4:40 **Lens Proteins**
ROBERT A. RESNIK

ANNUAL BANQUET, BAROQUE ROOM, BELMONT PLAZA HOTEL

7:00 P.M.

Thursday, June 6, 1957

1:30 **Solution of the Differential Equations Pertaining to Aqueous Humor Dynamics**
SAMUEL I. ASKOVITZ

2:00 **The Effects of Ganglionic Blocking Blood on Aqueous Flow in Normal and Glaucomatous Subjects**
DAVID A. ROSEN

2:20 **The Aqueous: Plasma Steady-State Ratios of Potassium and Sodium and the Influence of Diamox and Dibenamine Thereon**
JOHN E. HARRIS, A. EUGENE CARLSON, LOUISE GRUBER, and GERTRUDE HOSKINSON

2:40 **Studies on the Mode of Action of Pilocarpine on Aqueous Outflow: Correlation of Tonographic and Gonioscopic Data with Histologic Studies of the Trabecular Meshwork of Monkey Eyes**
MILTON FLOCKS and H. CHRISTIAN ZWENG

3:00 **Dynamics of Diamox Induced Bicarbonate Changes in Aqueous Humor of Rabbit Eye**
HARRY GREEN, MAYER J. MANN, SAMUEL I. ASKOVITZ, and IRVING H. LEOPOLD

3:20 **Intermission**

3:40 **The Bicarbonate Concentration of Guinea Pig Aqueous Humor: Effect of Scurvy and of Acetazolamide**
BERNARD BECKER

4:00 **The Tritium Steady State of the Rabbit Eye**
FRANK W. NEWELL

4:20 **Proctor Medal Recipient**

ANNOUNCEMENTS

Orthoptics for Technicians.—The Basic Course in Orthoptics for Technicians, sponsored by the American Orthoptic Council, will be held in the Department of Ophthalmology, University Hospitals, Iowa City, from June 19 through Aug. 10, 1957. As usual, there will be didactic lectures and practical demonstrations, given by an outstanding faculty.

West Virginia Academy of Ophthalmology and Otolaryngology.—The annual meeting of the West Virginia Academy of Ophthalmology and Otolaryngology will be held at the Greenbrier, White Sulphur Springs, West Virginia, May 31 through June 1, 1957.

Examination of Orthoptic Technicians.—The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in August and October, 1957. The written examination will be nonassembled and will take place on Thursday, Aug. 22, in certain assigned cities and will be proctored by designated ophthalmologists. The oral and practical examinations will be on Saturday, Oct. 12, in Chicago, just preceding the meeting of the American Academy of Ophthalmology and Otolaryngology.

Application for examination will be received by the office of the Chairman of Examinations, Dr. Frank D. Costenbader, 1605 22d St., N.W., Washington 8, D. C., and must be accompanied by the examination fee of $30. Applications will not be accepted after July 1, 1957.

Books

Histamine: Ciba Foundation Symposium, Jointly with the Physiological Society and the British Pharmacological Society. Price, $9.00. Pp. 472, including index, with many illustrations, not numbered. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

The Ciba Foundation symposia are well-known throughout the scientific world as gathering together and correlating the latest findings of internationally known authorities on a particular subject. Ophthalmologists working in the research fields which come into contact with histamines will be interested in the appearance of this authoritative monograph, dedicated to Sir Henry Dale.

The Office Assistant. By Portia M. Frederick and Carol Towner. Price, $4.75. Pp. 351, with 55 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

This very practical book on office practice should be helpful to the ophthalmologist. The details of secretarial duties and the techniques of office nursing are clearly and simply described, and an intelligent girl who reads this book carefully should learn much which will help her become a competent secretary, bookkeeper, technician, and public relations agent. There are good chapters on the keeping of medical records, how to answer the telephone and make appointments, handling of mail, filing of records, billing and collecting procedures, bookkeeping, banking, and advice on how to cope tactfully with all types of persons in the office. While much of the material may seem to be almost common sense, it is surprising how many girls new to a physician's office need to have some of these details pointed out to them. The authors are particularly qualified to write this book. Miss Frederick is an instructor in the Long Beach City College in Medical Office Assisting, and Miss Towner is the Executive Assistant, Department of Public Relations, American Medical Association.

On Parallax and Variations in the Stereoscopic Image. By Tauno Mannila. Price, not given. Pp. 107. Oy Tilgmann Ab, Helsinki, 1956.

This monograph deals with experiments in stereofluorography and stereofluoroscopy and is of interest to both ophthalmologists and roentgenologists. The chief interest to the ophthalmologists will be the bearing the subject has on ocular physiology, particularly in the field of depth perception.

Cryptococcosis. By M. L. Littmann, M.D., and Lorenz E. Zimmerman, M.D. Price, $8.50. Pp. 205, with 82 illustrations and 4 color plates. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1956.

This is a comprehensive atlas and text on one of the mycoses. With the ever-increasing importance of fungus disease, the authors have set themselves the task of publishing a series of monographs on the individual systemic mycoses. This is the first of the series. It covers cryptococcosis in all its aspects, both in man and in animals. The book will obviously be of chief use to laboratory workers in this field. The human form of the disease will be of interest to ophthalmologists in that papilledema and retinal exudates are commonly seen in cryptococcal infection of the central nervous system. The illustrations are excellent, and the book will undoubtedly be the authoritative reference for this field.

Diabetes Mellitus. By Howard F. Root, M.D., and Priscilla White, M.D. Price, $7.00. Pp. 346. McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36, 1956.

This is the fifth volume of a series of handbooks for the general practitioner by two of the best known specialists in diabetes in the country. Chapter 13 deals with the treatment of eye disorders due to diabetes, but, as might be expected, the only advice offered is "the treatment of retinitis as prevention."

Ocular Surgery. By H. Arruga, translated from the full Spanish edition by Michael J. Hogan and Luis Chaparro. Second English edition. Price, $48.00. Pp. 948 with 1309 illustrations (123 in color). McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1956.

The review of the first edition of this book in the ARCHIVES OF OPHTHALMOLOGY called attention to the fact that no more beautiful illustrations of surgical procedures had ever appeared in an English text. This second edition maintains the high caliber of the first and in addition adds many new techniques and modifications of old ones which have appeared in the literature of the last few years. There are 1309 illustrations in the text, 123 in color. If this book were published merely as an atlas it would still be a real contribution to ophthalmic surgery.

Doctors Hogan and Chaparro have been able to make a translation from the Spanish which bears no resemblance to the usual English translation of foreign articles, in that they have maintained an easy, readable style in good idiomatic English. Only too frequently, translations can be easily recognized by awkward, overly padded sentences which take so long to read, and which say so little. The exposition of surgical procedures should be concise and carefully worded, so that a picture of the various steps in the procedure comes to the mind of the reader as naturally as though he were seeing a moving picture. This text achieves just that.

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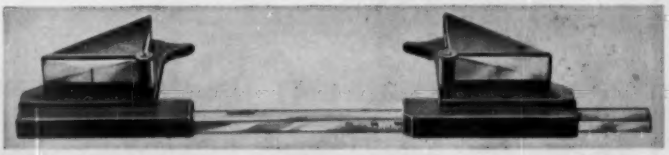

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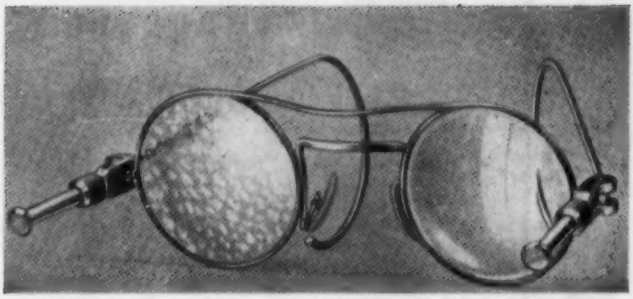

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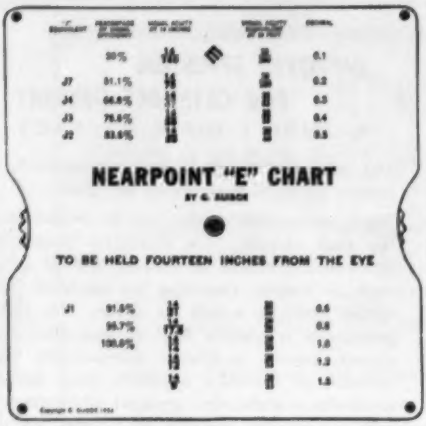

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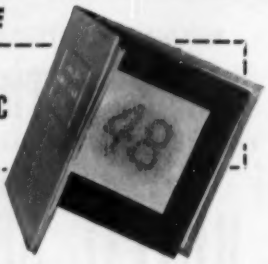

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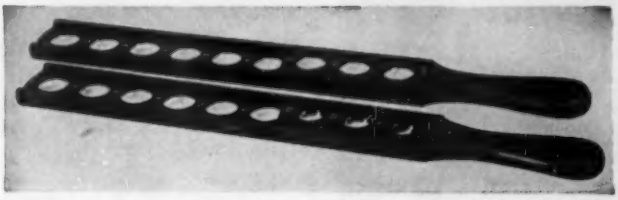

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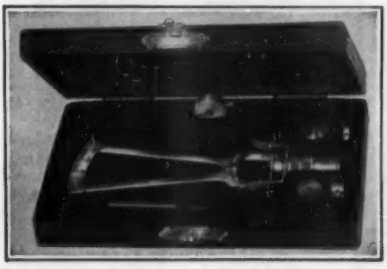

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*Patent No. 2,653,327

Phantom diagram showing vertical and horizontal rectus muscles sutured in position.

Diagram showing position of the prosthetic eye in relation to implant, socket and caruncle.

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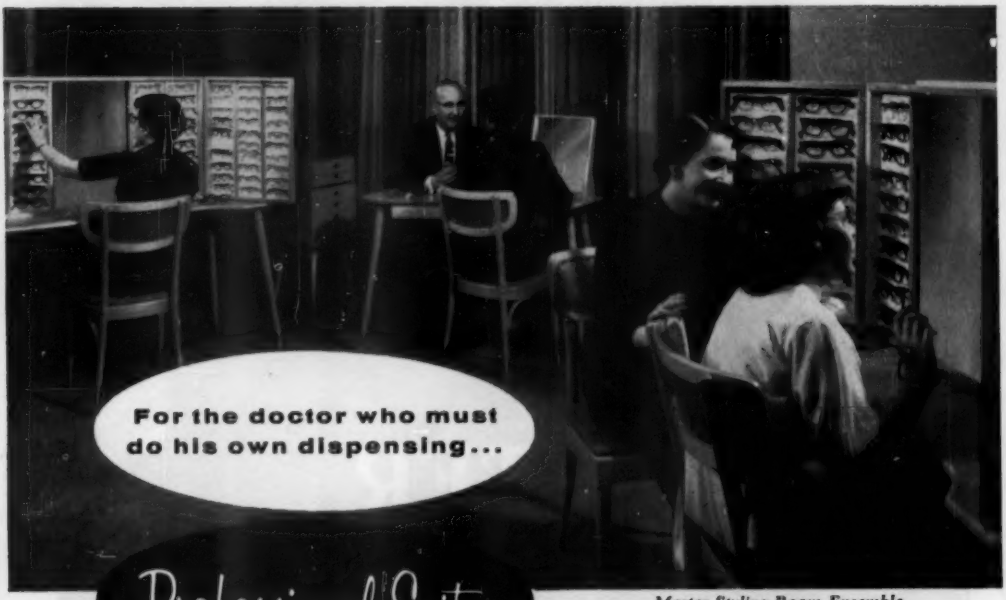

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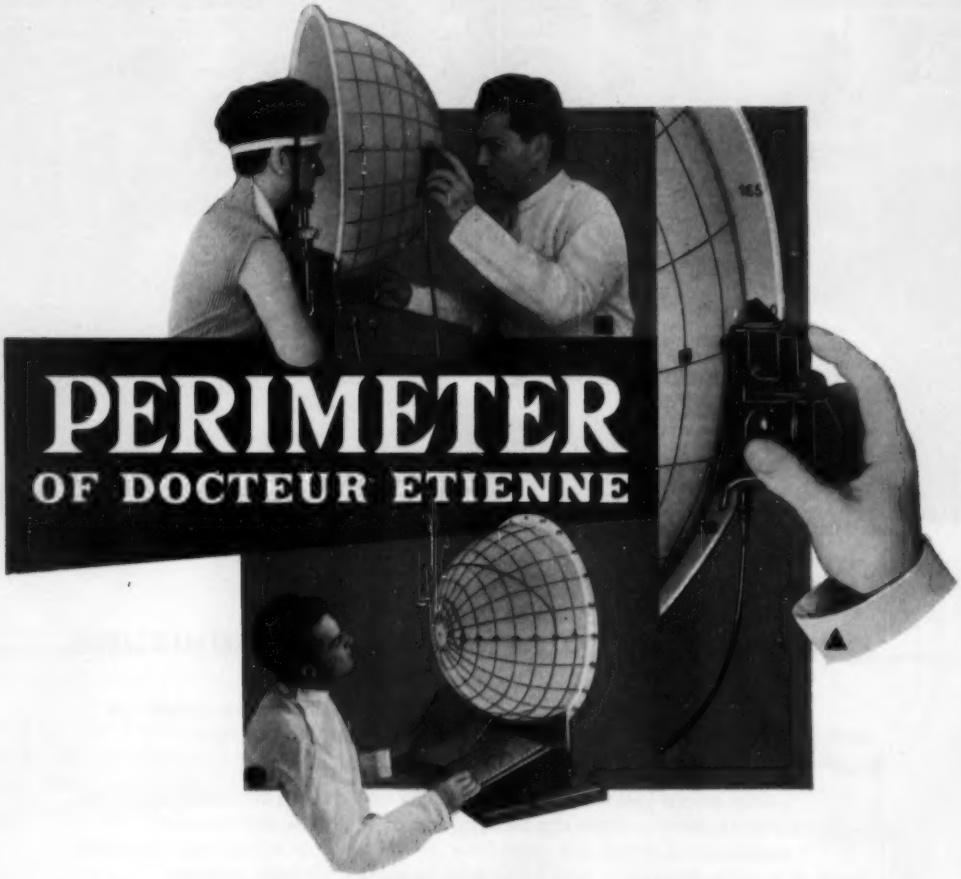

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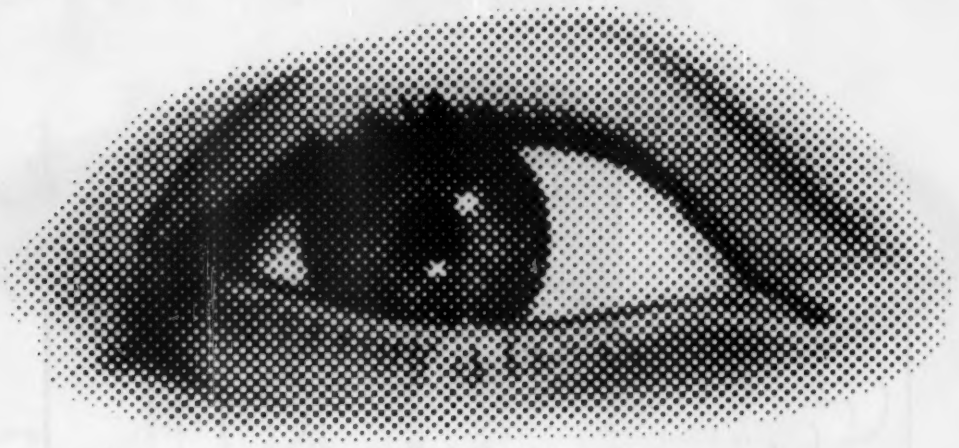

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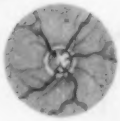

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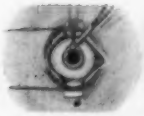

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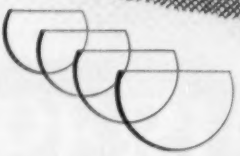

D Segment

Straight-top bifocal with 20, 22, 25 and 28mm segment widths. In 20 and 22mm segments, Vision-Ease D is a standard for the majority of normal presbyopic cases. The larger-field 25 and 28mm segments, however, are especially useful where greater reading area or near field is desirable or necessary. All segment sizes are on a full 58mm-round blank.

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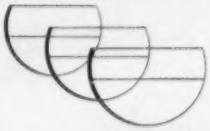

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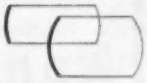

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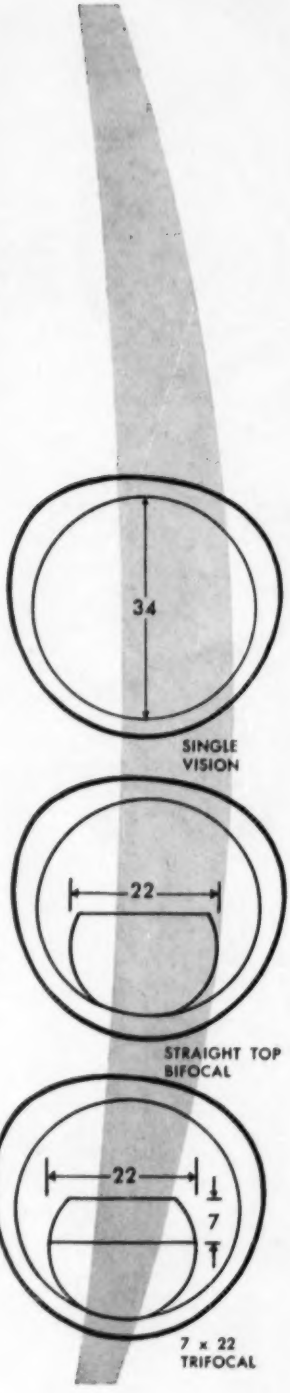

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